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(54) **MIRNAS AS NOVEL THERAPEUTIC TARGETS AND DIAGNOSTIC BIOMARKERS FOR PARKINSONS DISEASE**

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(51) **Int. Cl.**

C12Q 1/68	(2006.01)
C07H 21/02	(2006.01)
C07H 21/04	(2006.01)
C12N 15/113	(2010.01)

(52) **U.S. Cl.**
CPC ***C12Q 1/6883*** (2013.01); ***C12N 15/113*** (2013.01); *C12N 2310/113* (2013.01); *C12Q 2600/158* (2013.01); *C12Q 2600/16* (2013.01); *C12Q 2600/178* (2013.01)

(58) **Field of Classification Search**
CPC C12N 2310/11; C12N 15/113
See application file for complete search history.

(56) **References Cited**

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(57) **ABSTRACT**

The disclosure provides pharmaceutical compositions including an oligonucleotide that down-regulates the over-expression of at least one miRNA of SEQ ID NOs: 1-283. The oligonucleotide may be complementary to the nucleotide sequence of at least one of SEQ ID NOs: 1-283, or hybridizes under stringent conditions to a nucleotide sequence of at least one of SEQ ID NOs: 1-283. Further provided are methods of diagnosing Parkinson's Disease (PD) in a subject. The methods may include detecting the level of expression of at least one miRNA of SEQ ID NOs: 1-283 in a biological sample from the subject, and comparing the level of expression in the sample to the level of expression in a reference. Further provided are methods for treating, preventing, or reducing the risk of PD. Kits are also provided.

6 Claims, 11 Drawing Sheets

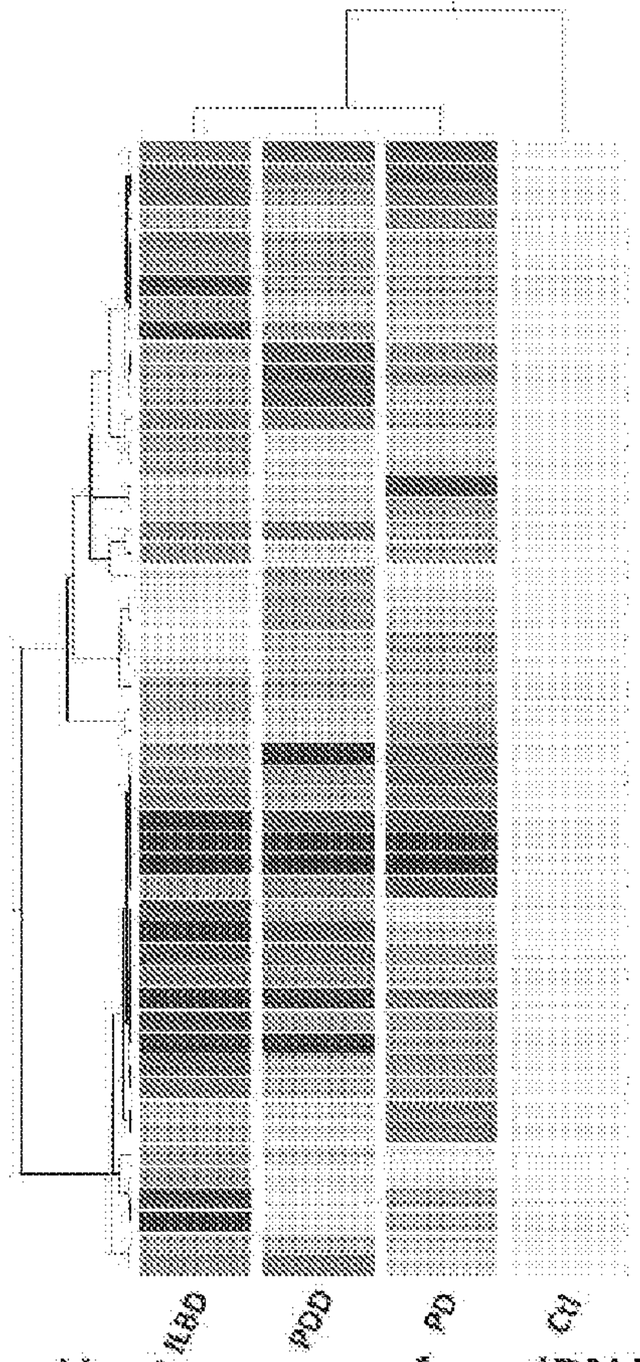


Figure 1. Heat-maps of miRNAs Differentially Expressed in the Putamen *By clinical diagnosis.*

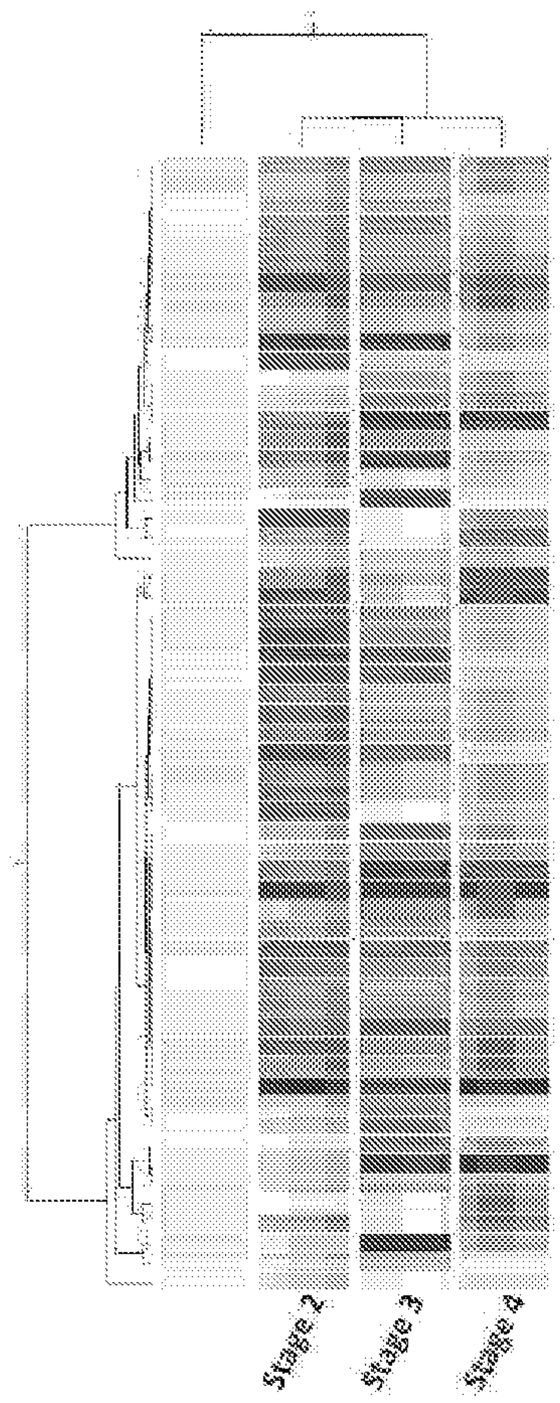


Figure 2. Heat-maps of miRNAs Differentially Expressed in the Putamen *By Unified staging system for LBD* .

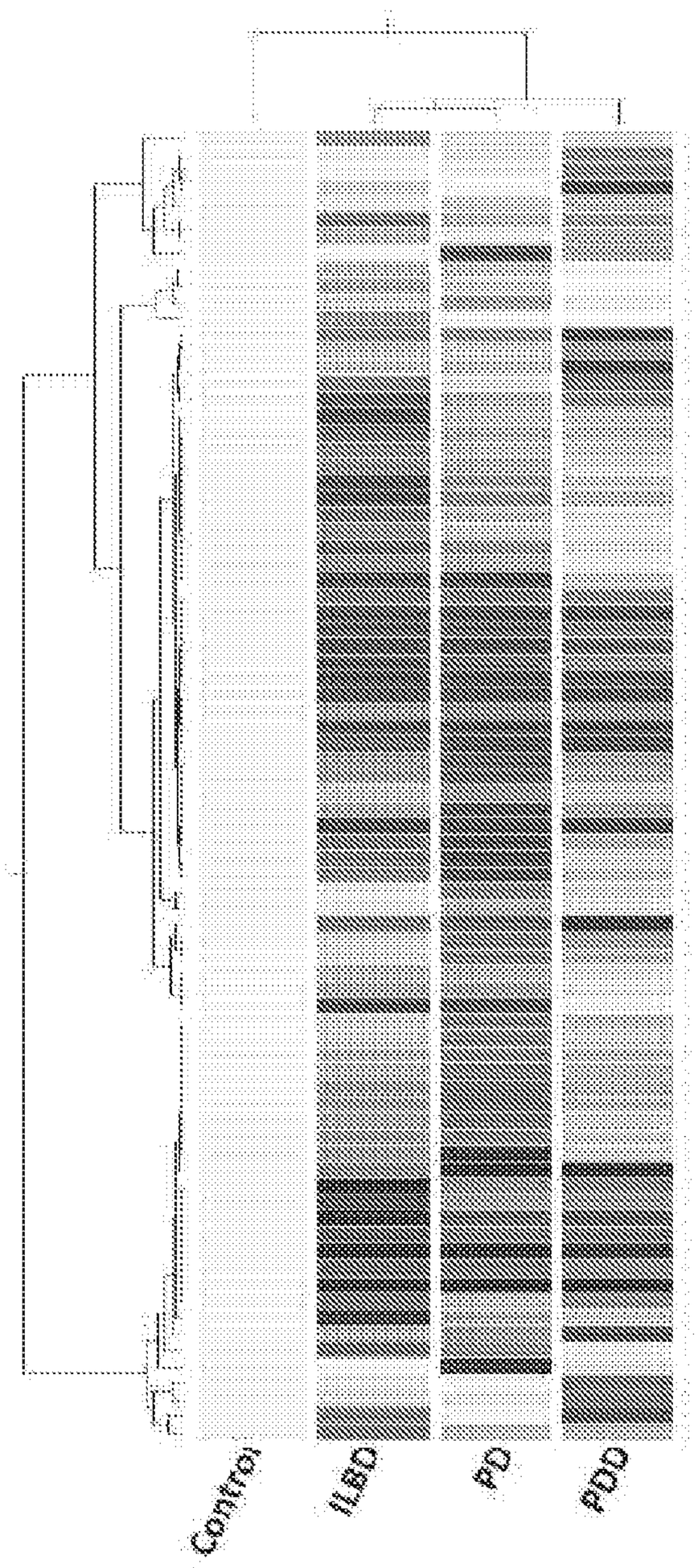


Figure 3. Heat-map of miRNAs Differentially Expressed in CSF *By clinical diagnosis.*

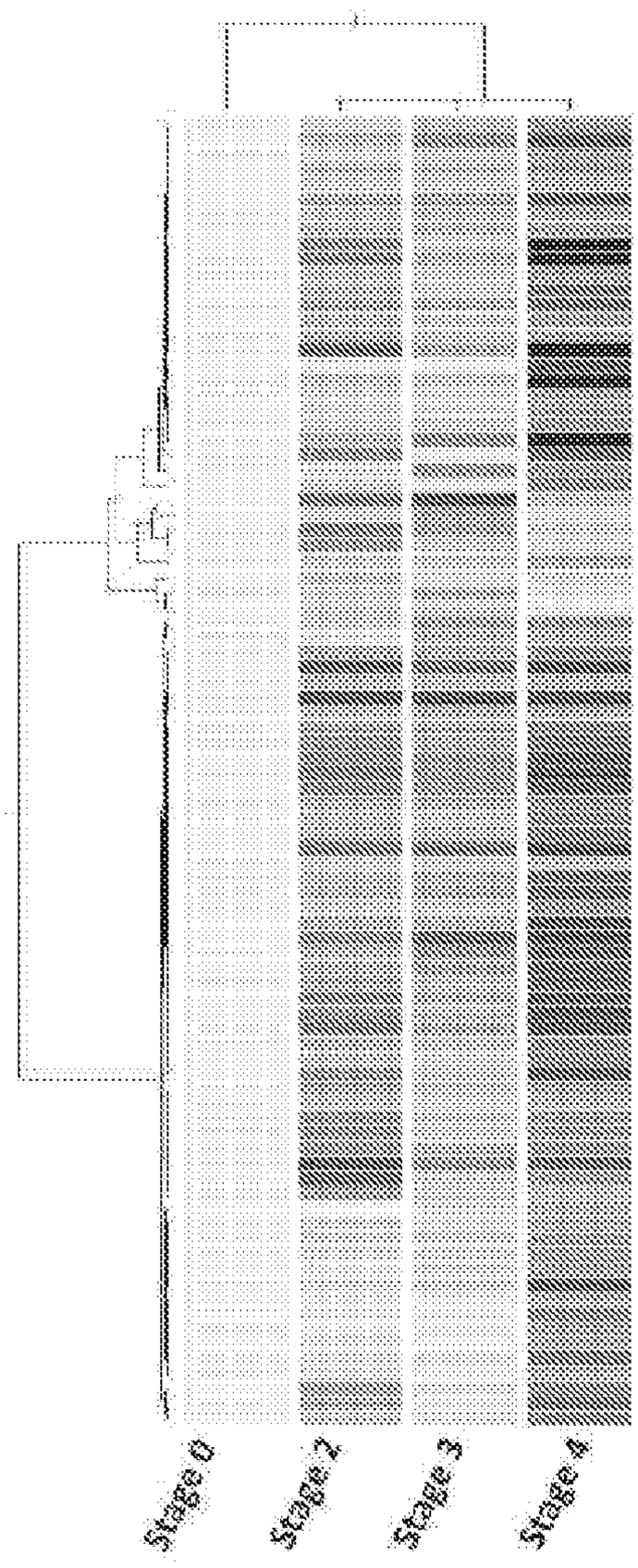
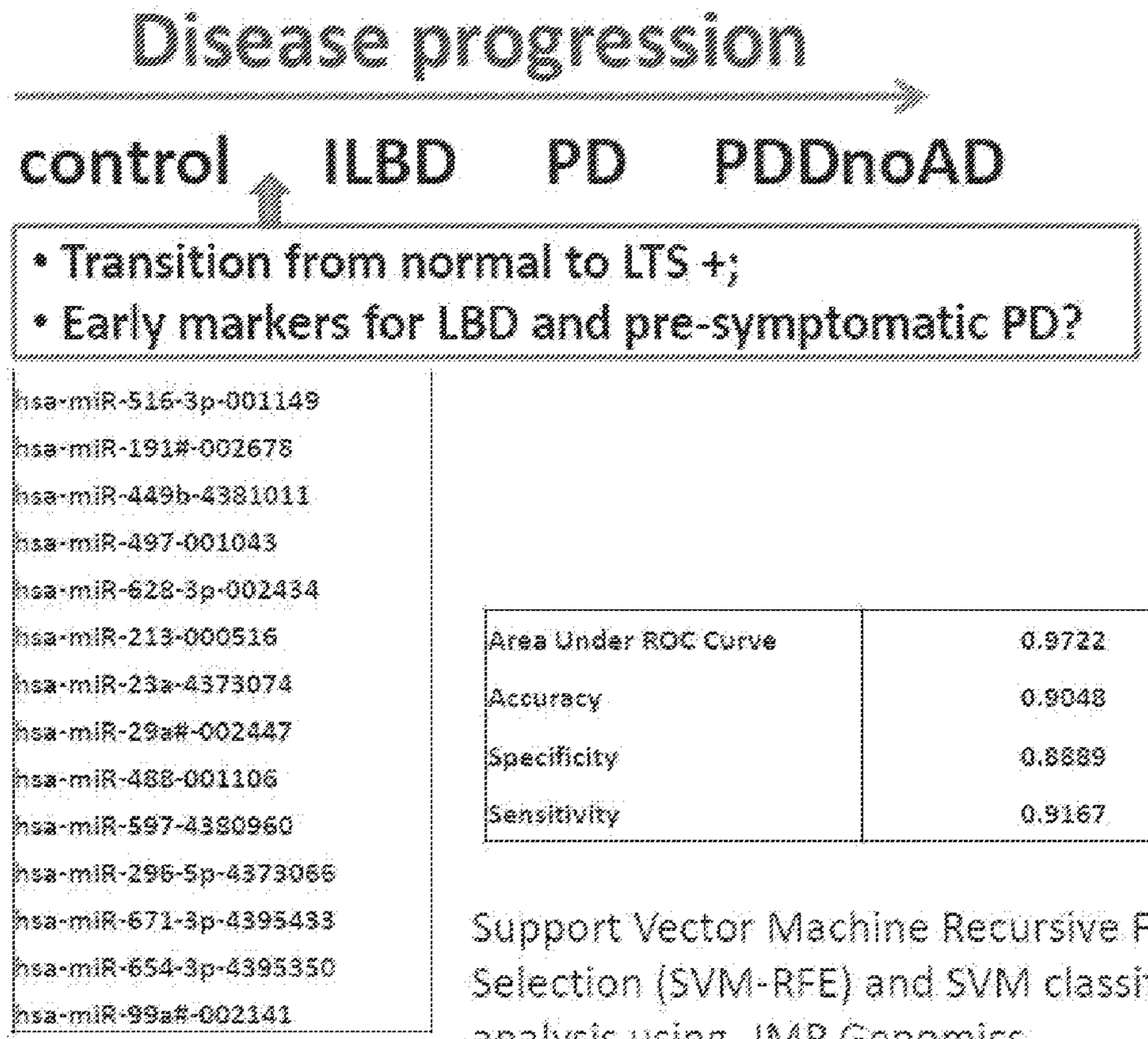


Figure 4. Heat-map of miRNAs Differentially Expressed in CSF by *Unified Staging System of LBDs*.

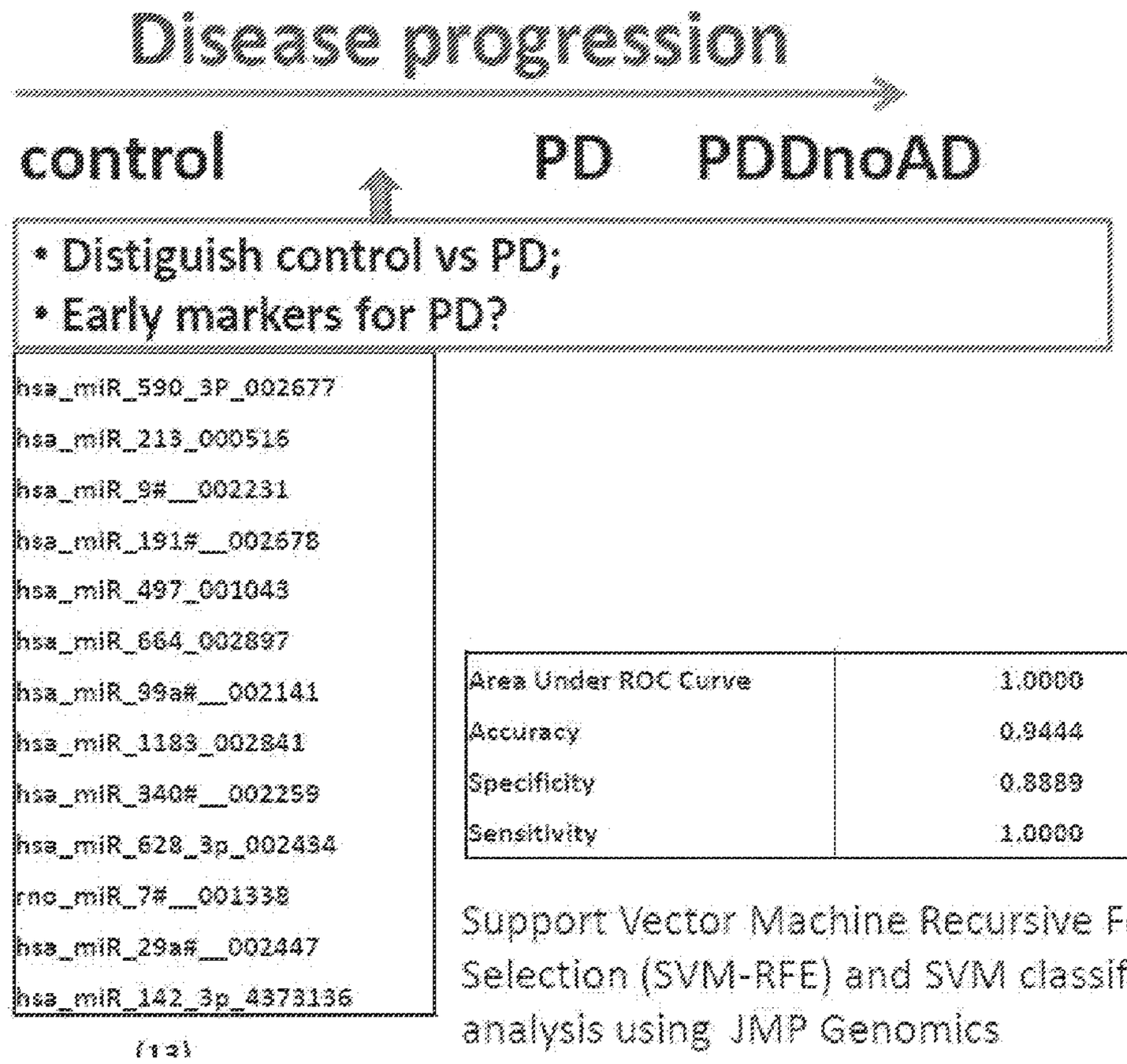
Figure 5. miRNA Signatures Which Reflect the Onset of LB Pathology



Area Under ROC Curve	0.9722
Accuracy	0.9048
Specificity	0.8889
Sensitivity	0.9167

Support Vector Machine Recursive Feature Selection (SVM-RFE) and SVM classification analysis using JMP Genomics

Figure 6. miRNA Signatures Which Reflect the Onset of LB Pathology



Area Under ROC Curve	1.0000
Accuracy	0.9444
Specificity	0.8889
Sensitivity	1.0000

Support Vector Machine Recursive Feature Selection (SVM-RFE) and SVM classification analysis using JMP Genomics

Figure 7. miRNA Signatures Which may Reflect the Onset of PD

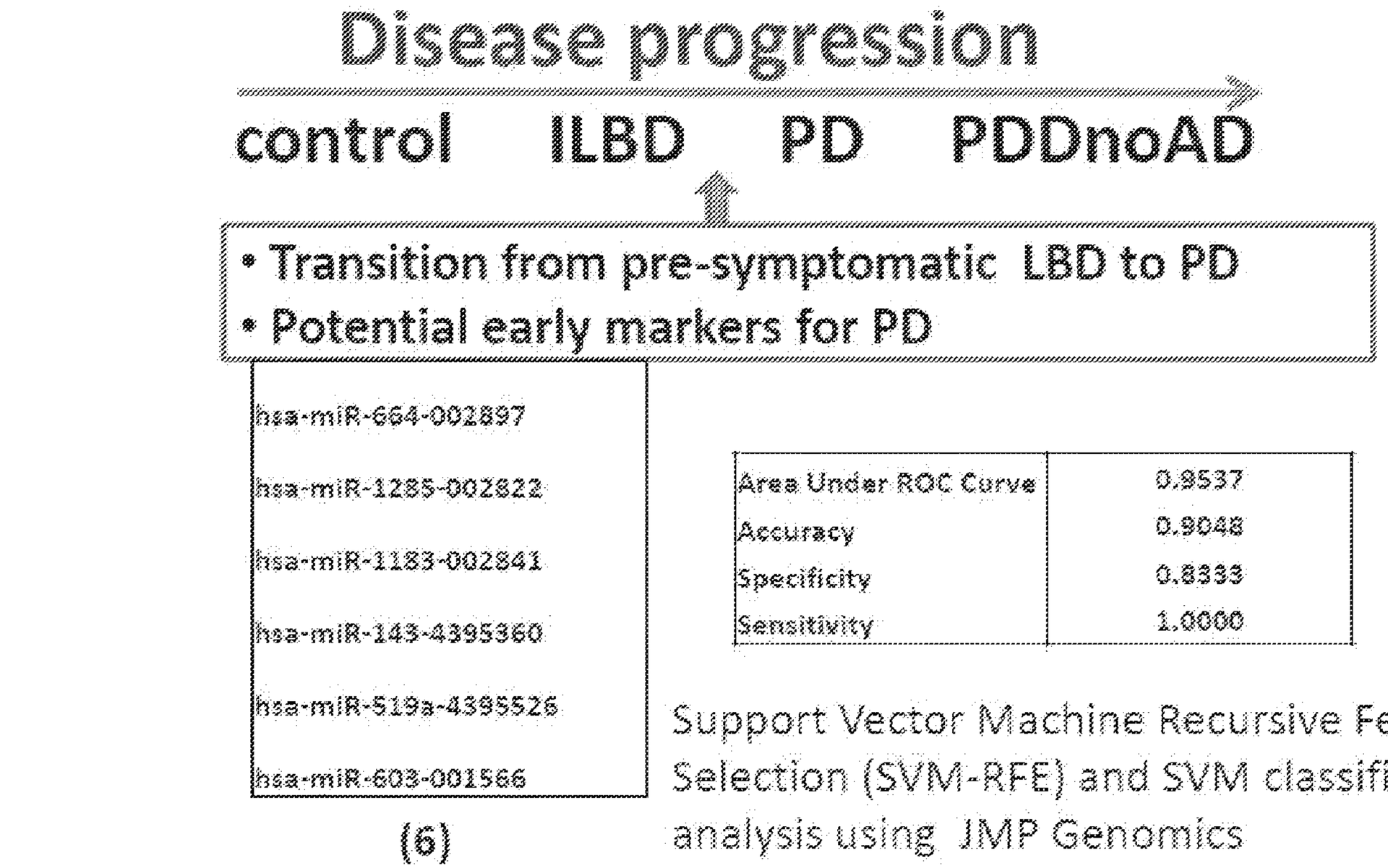


Figure 8. miRNA Signatures Which may Reflect the Onset of PD

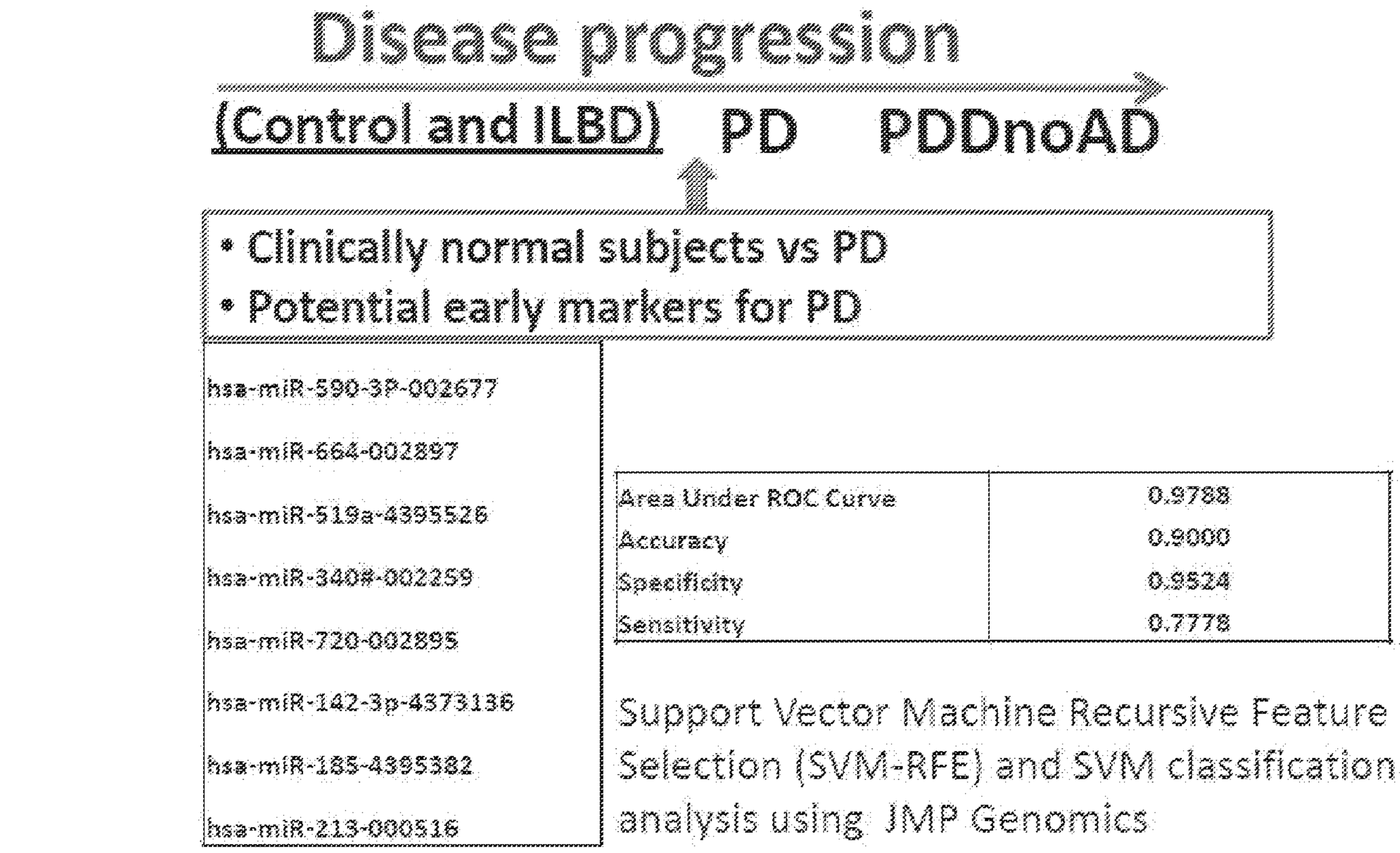
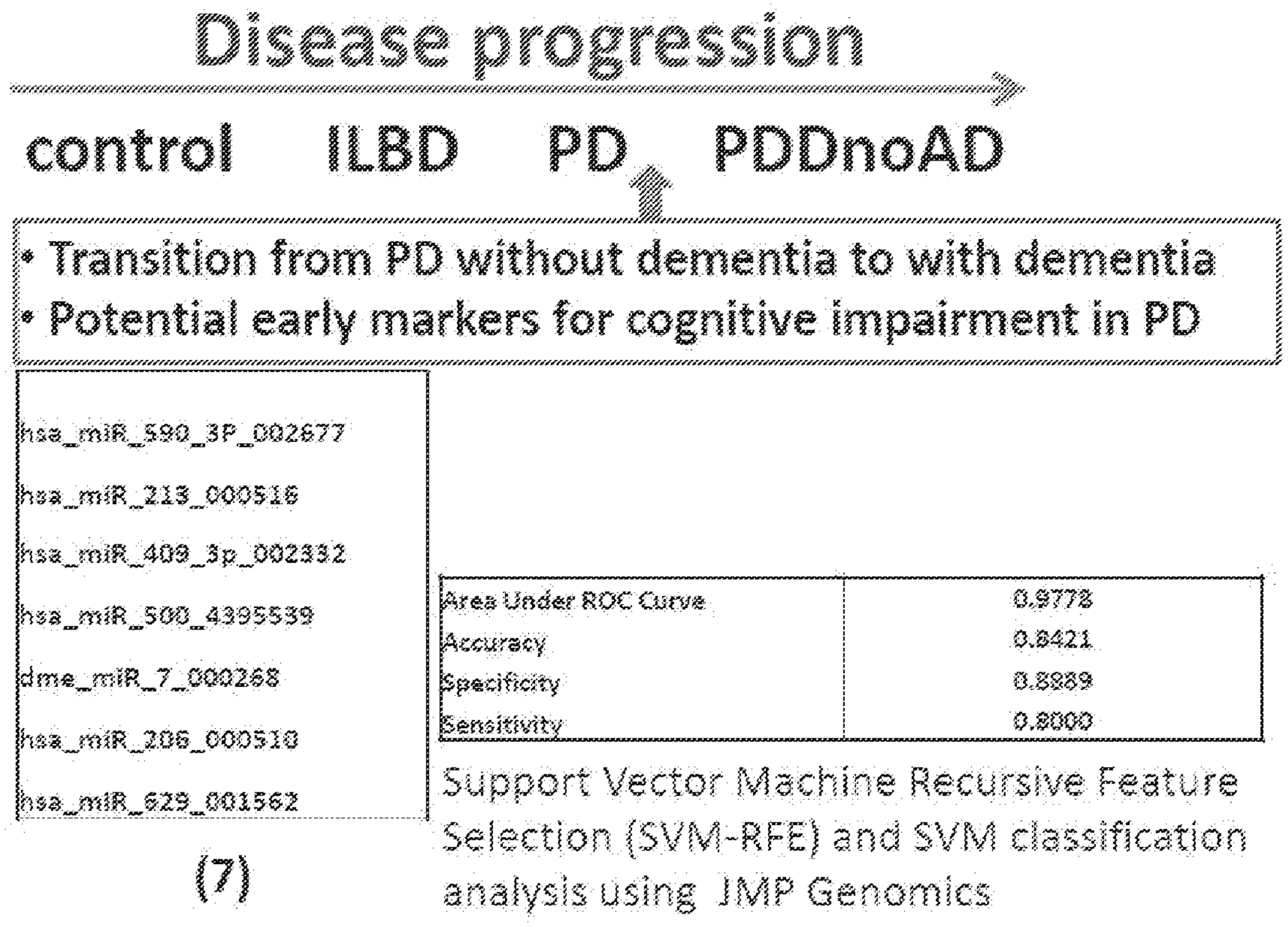


Figure 9. miRNA Signatures Reflecting the Onset of Cognitive Impairment in PD



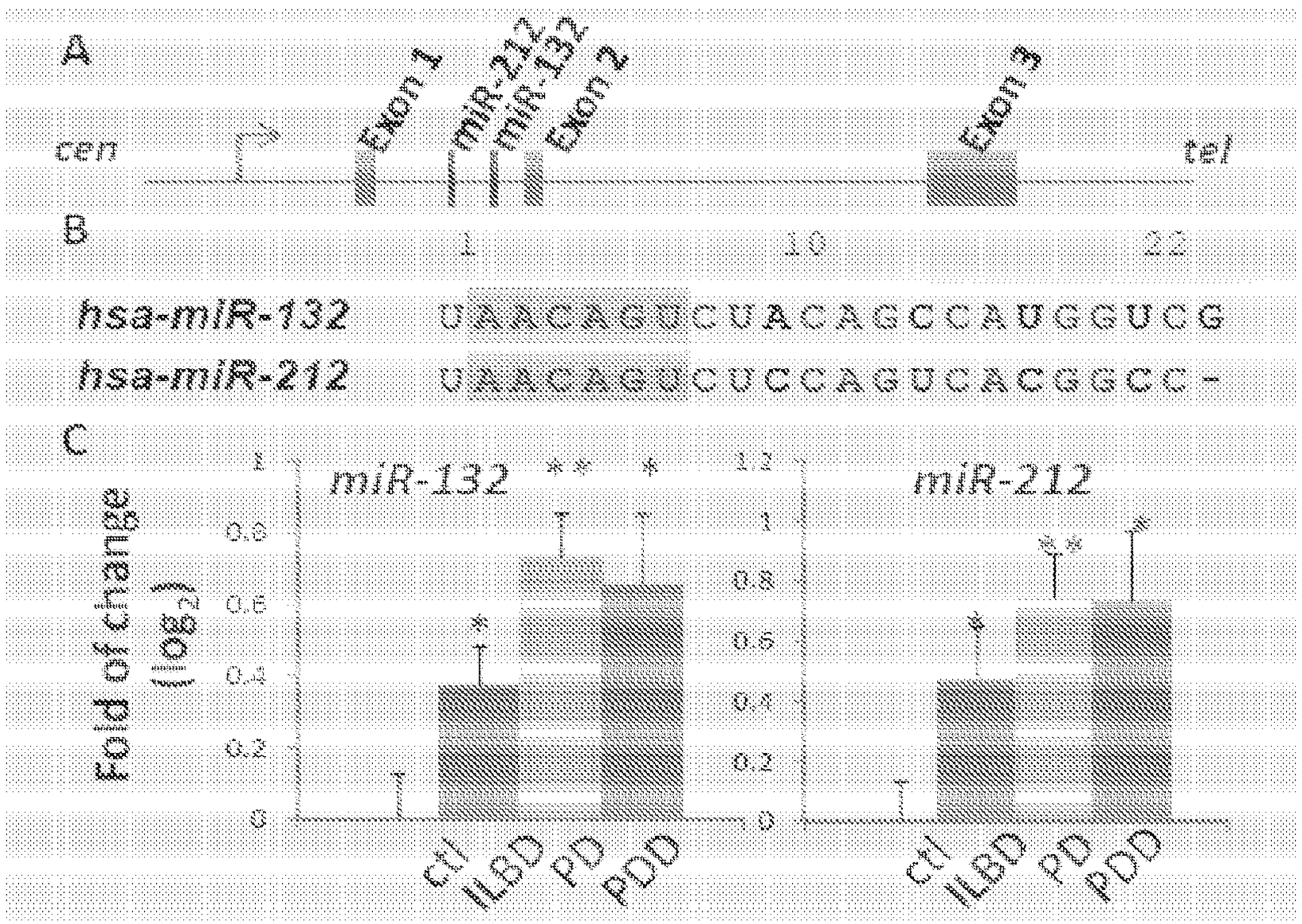


Figure 10. A. Genomic organization of miR-212/132 in the first intron of a non-coding RNA gene on human Chr1p13.3. B. Alignment of mature sequence of human miR-132 and miR-212, which share the same seed sequences (in green rectangular box). C. Relative expression levels of miR-132 and miR-212 in the putamen of normal control (Ctl), iLBD, PD and PDD subjects. The y-axis is in $\log_2$ phase. *: $p<0.05$; **: $p<0.01$ when compared to controls.

miR-132 (SEQ ID NO: 79); miR212 (SEQ ID NO: 124)

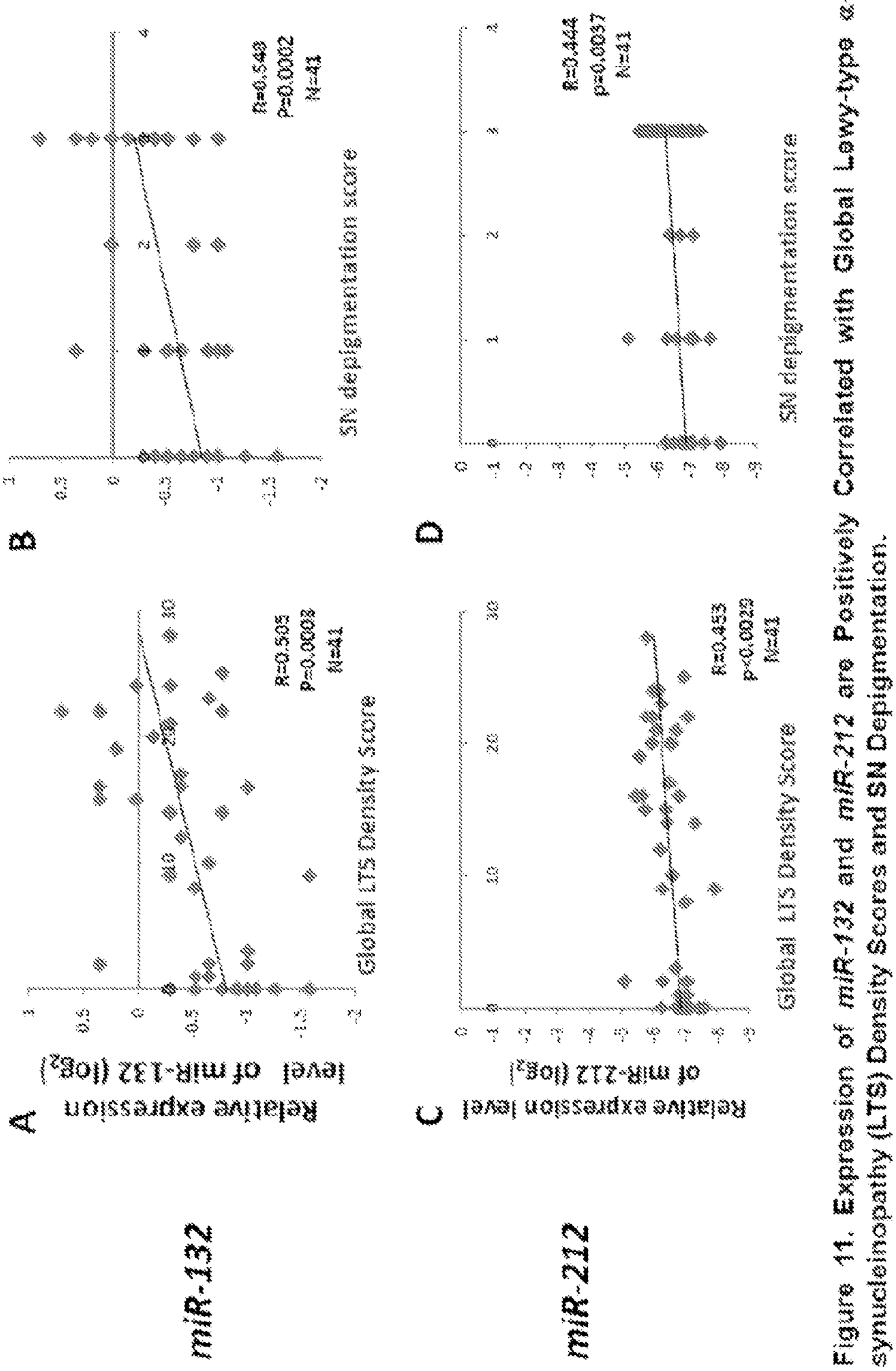


Figure 11. Expression of *miR-132* and *miR-212* are Positively Correlated with Global Lewy-type α-synucleinopathy (LTS) Density Scores and SN Depigmentation.

MIRNAS AS NOVEL THERAPEUTIC TARGETS AND DIAGNOSTIC BIOMARKERS FOR PARKINSONS DISEASE

This application claims the benefit under 35 U.S.C. §371 of International Application No. PCT/US2013/051849, filed Jul. 24, 2013, which claims the benefit of U.S. Provisional Application No. 61/675,603, filed Jul. 25, 2012, which are incorporated by reference herein in their entirety.

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/675,603, filed Jul. 25, 2012, which is incorporated by reference herein in its entirety.

FIELD

This disclosure relates to therapeutic and diagnostic markers for Parkinson's Disease.

INTRODUCTION

MicroRNAs (miRNAs) are small, non-coding, regulatory RNAs of 18-24 nucleotides in length. Mature miRNAs regulate messenger RNAs (mRNAs) of their downstream target genes by base-pairing to their target sites to specify cleavage of the target mRNAs or to destabilize the mRNA and/or repress translation of the targeted mRNA. miRNAs are expressed in the nervous system and modulate large numbers of neuronal genes, playing important roles in neurogenesis and neurodegenerative diseases. Besides being a major level of gene expression regulation, miRNAs also are recognized as excellent biomarkers for various diseases, especially in the diagnosis and prognosis of cancer. However, the roles of miRNAs in the pathogenesis of Parkinson's Disease and their potential as biomarkers for Parkinson's Disease have not being fully studied.

SUMMARY

In some aspects, the disclosure relates to pharmaceutical compositions including an oligonucleotide that down-regulates the over-expression of at least one miRNA of SEQ ID NOs: 1-283. The oligonucleotide may be a) complementary to the nucleotide sequence of at least one of SEQ ID NOs: 1-283, or b) hybridizes under stringent conditions to a nucleotide sequence of at least one of SEQ ID NOs: 1-283.

In further aspects, the disclosure relates to methods of diagnosing Parkinson's Disease (PD) in a subject. The methods may include detecting the level of expression of at least one miRNA of SEQ ID NOs: 1-283 in a biological sample from the subject, and comparing the level of expression in the sample to the level of expression in a reference. An increased or decreased level of expression in the sample compared to the level of expression in the reference may identify the subject as having PD or who is at risk of developing PD. In some aspects, a miRNA signature may be used to diagnose a subject at risk for developing or having PD.

Another aspect of the disclosure provides methods for treating, preventing, or reducing the risk of PD associated with aberrant expression of a miRNA in a cell, tissue, or animal, the method comprising contacting the cell, tissue, or animal with a pharmaceutical composition including an oligonucleotide that down-regulates the over-expression of at least one miRNA of SEQ ID NOs: 1-283. The oligonucleotide may be a) complementary to the nucleotide sequence of at least one of SEQ ID NOs: 1-283, or b) hybridizes under stringent conditions to a nucleotide sequence of at least one of SEQ ID NOs: 1-283.

In yet another aspect of the disclosure, kits are provided for performing measurement of a miRNA signature, the miRNA signature comprising at least one miRNA of SEQ ID NOs: 1-283, wherein the kit comprises reagents for measuring an expression level of at least one miRNA of SEQ ID NOs: 1-283.

The disclosure provides for other aspects and embodiments that will be apparent in light of the following detailed description and accompanying Figures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a heat-map of miRNAs differentially expressed in the putamen by clinical diagnosis.

FIG. **2** is a heat-map of miRNAs differentially expressed in the putamen by unified staging system for Lewy-body disorders (LBDs).

FIG. **3** is a heat-map of miRNAs differentially expressed in cerebrospinal fluid (CSF) by clinical diagnosis.

FIG. **4** is a heat-map of miRNAs differentially expressed in CSF by unified staging system of LBDs.

FIG. **5** is a diagram of miRNA signatures that may be used to reflect the onset of Lewy body (LB) pathology.

FIG. **6** is a diagram of miRNA signatures that may be used to reflect the onset of LB pathology.

FIG. **7** is a diagram of miRNA signatures that may be used to reflect the onset of PD.

FIG. **8** is a diagram of miRNA signatures that may be used to reflect the onset of PD.

FIG. **9** is a diagram of miRNA signatures that may be used to reflect the onset of cognitive impairment in PD.

FIG. **10** is a diagram of the genomic organization of miR-212/132 in the first intron of a non-coding RNA gene on human Chr1p13.3.

FIGS. **11**A-D are graphs of the expression of miR-132 and miR-212.

DETAILED DESCRIPTION

In a broad sense, the disclosure relates to therapeutic and diagnostic markers for Parkinson's Disease (PD). The pres-

ent invention relates to the discovery of differential expression levels of various miRNAs in PD compared to normal tissue.

miRNAs are newly recognized, small, regulatory RNAs, which regulate gene expression by repressing translation and/or break down mRNAs of their downstream target genes. Misregulation of miRNAs in the central nervous system contributes to neurodegenerative disorders. To identify miRNAs involved in the pathogenesis of PD, fresh frozen putamen and cerebrospinal fluid (CSF) samples of 10 normal control, 12 (ILBD), 10 PD, and 10 PD with dementia but no Alzheimer's disease (AD) (PDDnoAD) cases were obtained from the Sun Health Research Institute (SHRI) (Table 1 and Table 2). By Unified Staging System for Lewy body diseases (LBDs), besides 9 normal controls, these samples include 12 Stage 2, 9 Stage 3, and 11 Stage 4 samples, representing increasing severity of the diseases.

TABLE 1

Subjects Classified by Clinical Diagnosis and Unified Staging System for LBDs (USSLBD)

	Stages				
Diagnosis	Stage 0	Stage 2	Stage 3	Stage 4	total
Control	9				9
ILBD		7	5		12
PD		3	2	5	10
PDD no AD		2	2	6	10
Total	9	12	9	11	41

Beach T G et al. Unified staging system for Lewy body disorders (LBDs): correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. Acta Neuropathol. 2009, 117; 613-634.
Classification of subjects with LBDs by Lewy-type α-synucleinopathy (LTS) distributions:
Stage 0: No LTS. Control group.
Stage 1: Olfactory bulb only;
Stage 2: Brainstem or Limbic predominant;
Stage 3: Brainstem and Limbic;
Stage 4: Neocortical.

Subsequently, miRNA-proof total RNA from all putamen and CSF samples was isolated using a mirVana™ miRNA isolation system (Life Technologies). On average, 0.69+/−0.06 μg of total RNA/mg putamen tissue (n=41); and 2.74+/−0.21 μg of total RNA/mL CSF samples (n=41) was obtained. There was no significant difference in quantity of total RNA isolated from different diagnostic groups. Subsequently, miRNA profiling in all putamen (n=41) and CSF total RNA (n=41) was performed using the Taqman miRNA microarrays (Applied Biosystem), which detected 754 known human miRNAs in total, to establish miRNA transcriptomes of the putamen and CSF of all 41 cases.

By comparison of these miRNA-expression profiles, miRNAs differentially expressed in the putamen and CSF among different groups classified by clinical diagnosis, by Unified Staging System for LBD, and by the extent of Substantia Nigra (SN) neuron depigmentation were identifed. As further detailed in the Examples, expression profiles were analyzed using a two-tailed t test between two groups. Significant differential expression was identified as $p<0.05$ and ≥2 fold changes, including both increased and decreased expression levels by ≥2 folds. Exemplary miRNAs (SEQ ID NOs: 1-283) are shown in Table 39. In some embodiments, at least one miRNA selected from SEQ ID NOs: 1-283 may have increased or decreased expression relative to a reference, control, or normal sample by at least about 1.5-fold, at least about 1.6-fold, at least about 1.7-fold, at least about 1.8-fold, at least about 1.9-fold, at least about 2.0-fold, at least about 2.1-fold, at least about 2.2-fold, at least about 2.3-fold, at least about 2.4-fold, at least about 2.5-fold, at least about 2.6-fold, at least about 2.7-fold, at least about 2.8-fold, at least about 2.9-fold, at least about 3.0-fold, at least about 3.1-fold, at least about 3.2-fold, at least about 3.3-fold, at least about 3.4-fold, at least about 3.5-fold, at least about 3.6-fold, at least about 3.7-fold, at least about 3.8-fold, at least about 3.9-fold, or at least about 4.0-fold.

TABLE 2

Main basic characteristics of the study subjects classified by clinical diagnosis.

	No.	age*	gender (% M)	ApoE-s4 (%)	PMI (mean +/− SD)	MMSE**	UPDRS***	SN pigmented neuron loss score****	α-Synuclein density score (average +/− SD)
control	9	82.1 +/− 6.8 (73-97)	60	22.0	2.4 +/− 0.6	29.0 (1.3) (9)	7.0 (5.4) (9)	none (6), mild (3)	0
ILBD	12	86.3 +/− 4.85 (73-91)	67	16.7	2.7 +/− 0.6	28.0 (1.7) (8)	7.0 (5.1) (7)	none (5), mild (3), mod (1), severe (3)	8.6 +/− 8.1
PD	10	79.4 +/− 5.9 (72-90)	55	18.2	6.2 +/− 4.2	26.8 (3.3) (4)	9.6 (14.9) (6)	mile (1), mod (2), severe (8)	18.0 +/− 5.3
PDD (no AD)	10	76.1 +/− 5.9 (69-84)	60	20.0	3.0 +/− 1.4	17.1 (10.0) (7)	25.3 (39.3) (6)	none (1), severe (9)	19.1 +/− 5.2

*age is presented by average +/− standard deviation (range);

**MMSE is presented by, average (standard deviation) (number of objects with MMSE data);

***UPDRS is presented by average (standard deviation) (number of objects with MMSE data), and was obtained from subjects who were in the "off state" with respect to dopaminergic therapeutic effects.

TABLE 39

Sequences of exemplary miRNAs.

	miRNA	Sequences	SEQ ID NO
miRNA signature distinguishing control vs PD	hsa_miR_590_3P_002677	UAAUUUUAUGUAUAAGCUAGU	1
	hsa_miR_213_000516	ACCAUCGACCGUUGAUUGUACC	2
	hsa_miR_9#_002231	AUAAAGCUAGAUAACCGAAAGU	3
	hsa_miR_191#_002678	GCUGCGCUUGGAUUUCGUCCCC	4
	hsa_miR_497_001043	CAGCAGCACACUGUGGUUUGU	5
	hsa_miR_664_002897	UAUUCAUUUAUCCCCAGCCUACA	6
	hsa_miR_99a#_002141	CAAGCUCGCUUCUAUGGGUCUG	7
	hsa_miR_1183_002841	CACUGUAGGUGAUGGUGAGAGUGGGCA	8
	hsa_miR_340#_002259	UCCGUCUCAGUUACUUUAUAGC	9
	hsa_miR_628_3p_002434	UCUAGUAAGAGUGGCAGUCGA	10
	rno_miR_7#_001338	CAACAAAUCACAGUCUGCCAUA	11
	hsa_miR_29a#_002447	ACUGAUUUCUUUUGGUGUUCAG	12
	hsa_miR_142_3p_4373136	UGUAGUGUUUCCUACUUUAUGGA	13
miRNA signature distinguishing (Control + ILBD) vs PD	hsa-miR-590-3P-002677	UAAUUUUAUGUAUAAGCUAGU	14
	hsa-miR-664-002897	UAUUCAUUUAUCCCCAGCCUACA	15
	hsa-miR-519a-4395526	AAAGUGCAUCCUUUUAGAGUGU	16
	hsa-miR-340#-002259	UCCGUCUCAGUUACUUUAUAGC	17
	hsa-miR-720-002895	UCUCGCUGGGGCCUCCA	18
	hsa-miR-142-3p-4373136	UGUAGUGUUUCCUACUUUAUGGA	19
	hsa-miR-185-4395382	UGGAGAGAAAGGCAGUUCCUGA	20
	hsa-miR-213-000516	ACCAUCGACCGUUGAUUGUACC	21
miRNA signature distinguishing ILBD vs PD	hsa-miR-664-002897	UAUUCAUUUAUCCCCAGCCUACA	22
	hsa-miR-1285-002822	UCUGGGCAACAAAGUGAGACCU	23
	hsa-miR-1183-002841	CACUGUAGGUGAUGGUGAGAGUGGGCA	24
	hsa-miR-143-4395360	UGAGAUGAAGCACUGUAGCUCA	25
	hsa-miR-519a-4395526	AAAGUGCAUCCUUUUAGAGUGU	26
	hsa-miR-603-001566	CACACACUGCAAUUACUUUUGC	27
miRNA signature distinguishing PD vs PDDnoAD	hsa_miR_590_3P_002677	UAAUUUUAUGUAUAAGCUAGU	28
	hsa_miR_213_000516	ACCAUCGACCGUUGAUUGUACC	29
	hsa_miR_409_3p_002332	GAAUGUUGCUCGGUGAACCCCU	30
	hsa_miR_500_4395539	UAAUCCUUGCUACCUGGGUGAGA	31
	dme_miR_7_000268	UGGAAGACUAGUGAUUUUGUUGU	32
	hsa_miR_206_000510	UGGAAUGUAAGGAAGUGUGUGG	33
	hsa_miR_629_001562	GUUCUCCCAACGUAAGCCCAGC	34
All miRNA differentially expressed and/or correlated with clinical/pathological findings	dme-miR-7-000268	UGGAAGACUAGUGAUUUUGUUGU	35
	hsa-let-7c-4373167	UGAGGUAGUAGGUUGUAUGGUU	36
	hsa-let-7d-4395394	AGAGGUAGUAGGUUGCAUAGU	37
	hsa-let-7f-1#-002417	CUAUACAAUCUAUUGCCUUCCC	38
	hsa-miR-100#-002142	CAAGCUUGUAUCUAUAGGUAUG	39
	hsa-miR-101#-002143	UACAGUACUGUGAUAACUGAA	40
	hsa-miR-101-4395364	CAGUUAUCACAGUGCUGAUGCU	41
	hsa-miR-105-4395278	UCAAAUGCUCAGACUCCUGUGGU	42
	hsa-miR-106b#-002380	CCGCACUGUGGGUACUUGCUGC	43
	hsa-miR-107-4373154	AGCAGCAUUGUACAGGGCUAUCA	44
	hsa-miR-10b-4395329	UACCCUGUAGAACCGAAUUUGUG	45
	hsa-miR-1183-002841	CACUGUAGGUGAUGGUGAGAGUGGGCA	46
	hsa-miR-1201-002781	AGCCUGAUUAAACACAUGCUCUGA	47
	hsa-miR-122-4395356	UGGAGUGUGACAAUGGUGUUUG	48
	hsa-miR-1224-3P-002752	CCCCACCUCCUCUCUCCUCAG	49
	hsa-miR-1226#-002758	GUGAGGGCAUGCAGGCCUGGAUGGGG	50
	hsa-miR-1227-002769	CGUGCCACCCUUUUCCCCAG	51
	hsa-miR-1233-002768	UGAGCCCUGUCCUCCCGCAG	52
	hsa-miR-1238-002927	CUUCCUCGUCUGUCUGCCCC	53
	hsa-miR-1244-002791	AAGUAGUUGGUUUGUAUGAGAUGGUU	54
	hsa-miR-124-4373295	UUAAGGCACGCGGUGAAUGCCA	55
	hsa-miR-1248-002870	ACCUUCUUGUAUAAGCACUGUGCUAAA	56
	hsa-miR-1255B-002801	CGGAUGAGCAAAGAAAGUGGUU	57
	hsa-miR-1256-002850	AGGCAUUGACUUCUCACUAGCU	58
	hsa-miR-125a-5p-4395309	UCCCUGAGACCCUUUAACCUGUGA	59
	hsa-miR-125b2#-002158	UCACAAGUCAGGCUCUUGGGAC	60
	hsa-miR-125b-4373148	UCCCUGAGACCCUAACUUGUGA	61
	hsa-miR-126#-000451	CAUUAUUACUUUUGGUACGCG	62
	hsa-miR-1260-002896	AUCCCACCUCUGCCACCA	63
	hsa-miR-1264-002799	CAAGUCUUAUUUGAGCACCUGUU	64
	hsa-miR-1269-002789	CUGGACUGAGCCGUGCUACUGG	65
	hsa-miR-1270-002807	CUGGAGAUAUGGAAGAGCUGUGU	66
	hsa-miR-1271-002779	CUUGGCACCUAGCAAGCACUCA	67
	hsa-miR-127-5p-4395340	CUGAAGCUCAGAGGGCUCUGAU	68
	hsa-miR-1282-002803	UCGUUUGCCUUUUUCUGCUU	69
	hsa-miR-1290-002863	UGGAUUUUUGGAUCAGGGA	70
	hsa-miR-1291-002838	UGGCCCUGACUGAAGACCAGCAGU	71

TABLE 39-continued

Sequences of exemplary miRNAs.

miRNA	Sequences	SEQ ID NO
hsa-miR-129-3p-4373297	AAGCCCUUACCCCAAAAAGUAU	72
hsa-miR-1298-002861	UUCAUUCGGCUGUCCAGAUGUA	73
hsa-miR-1300-002902	UUGAGAAGGAGGCUGCUG	74
hsa-miR-1301-002827	UUGCAGCUGCCUGGGAGUGACUUC	75
hsa-miR-1303-002792	UUUAGAGACGGGGUCUUGCUCU	76
hsa-miR-130a-4373145	CAGUGCAAUGUUAAAAGGGCAU	77
hsa-miR-130b-4373144	CAGUGCAAUGAUGAAAGGGCAU	78
hsa-miR-132-4373143	UAACAGUCUACAGCCAUGGUCG	79
hsa-miR-135a-4373140	UAUGGCUUUUUAUUCCUAUGUGA	80
hsa-miR-135b#-002159	AUGUAGGGCUAAAAGCCAUGGG	81
hsa-miR-135b-4395372	UAUGGCUUUUCAUUCCUAUGUGA	82
hsa-miR-136#-002100	CAUCAUCGUCUCAAAUGAGUCU	83
hsa-miR-137-4373301	UAUUGCUUAAGAAUACGCGUAG	84
hsa-miR-138-2#-002144	AGCUGGUGUUGUGAAUCAGGCCG	85
hsa-miR-138-4395395	GCUAUUUCACGACACCAGGGUU	86
hsa-miR-141-4373137	UAACACUGUCUGGUAAAGAUGG	87
hsa-miR-142-3p-4373136	UGUAGUGUUUCCUACUUUAUGGA	88
hsa-miR-143-4395360	UGAGAUGAAGCACUGUAGCUC	89
hsa-miR-14395333	UGGAAUGUAAAGAAGUAUGUA	90
hsa-miR-144#-002148	GGAUAUCAUCAUAUACUGUAAG	91
hsa-miR-144-002676	UACAGUAUAGAUGAUGUACU	92
hsa-miR-145#-002149	GGAUUCCUGGAAAUACUGUUCU	93
hsa-miR-145-4395389	GUCCAGUUUUCCCAGGAAUCCCU	94
hsa-miR-146a#-002163	CCUCUGAAAUUCAGUUCUUCAG	95
hsa-miR-146b-5p-4373178	UGAGAACUGAAUUCCAUAGGCU	96
hsa-miR-148a-4373130	UCAGUGCACUACAGAACUUUGU	97
hsa-miR-148b#-002160	AAGUUCUGUUAUACACUCAGGC	98
hsa-miR-149#-002164	AGGGAGGGACGGGGGCUGUGC	99
hsa-miR-151-5P-002642	UCGAGGAGCUCACAGUCUAGU	100
hsa-miR-153-4373305	UUGCAUAGUCACAAAAGUGA	101
hsa-miR-154#-000478	AAUCAUACACGGUUGACCUAUU	102
hsa-miR-15a-4373123	UAGCAGCACAUAAUGGUUUGUG	103
hsa-miR-181a2#-002317	ACCACUGACCGUUGACUGUACC	104
hsa-miR-181a-4373117	AACAUUCAACGCUGUCGGUGAGU	105
hsa-miR-183#-002270	UAUGGCACUGGUAGAAUUCACU	106
hsa-miR-183-4395380	GUGAAUUACCGAAGGGCCAUAA	107
hsa-miR-184-4373113	UGGACGGAGAACUGAUAAGGGU	108
hsa-miR-18a-4395533	UAAGGUGCAUCUAGUGCAGAUAG	109
hsa-miR-191#-002678	GCUGCGCUUGGAUUUCGUCCCC	110
hsa-miR-192-4373108	CUGACCUAUGAAUUGACAGCC	111
hsa-miR-193a-5p-4395392	UGGGUCUUUGCGGGCGAGAUGA	112
hsa-miR-195-4373105	UAGCAGCACAGAAAUAUUGGC	113
hsa-miR-196b-4395326	UAGGUAGUUUCCUGUUGUUGGG	114
hsa-miR-197-4373102	UUCACCACCUUCUCCACCCAGC	115
hsa-miR-198-4395384	GGUCCAGAGGGGAGAUAGGUUC	116
hsa-miR-199a-5p-4373272	CCCAGUGUUCAGACUACCUGUUC	117
hsa-miR-19b-4373098	UGUGCAAAUCCAUGCAAAACUGA	118
hsa-miR-200b-4395362	UAAUACUGCCUGGUAAUGAUGA	119
hsa-miR-202-4395474	AGAGGUAUAGGGCAUGGGAA	120
hsa-miR-203-4373095	GUGAAAUGUUUAGGACCACUAG	121
hsa-miR-206-000510	UGGAAUGUAAGGAAGUGUGUGG	122
hsa-miR-211-4373088	UUCCCUUUGUCAUCCUUCGCCU	123
hsa-miR-212-4373087	UAACAGUCUCCAGUCACGGCC	124
hsa-miR-213-000516	ACCAUCGACCGUUGAUUGUACC	125
hsa-miR-21-4373090	UAGCUUAUCAGACUGAUGUUGA	126
hsa-miR-217-4395448	UACUGCAUCAGGAACUGAUUGGA	127
hsa-miR-218-4373081	UUGUGCUUGAUCUAACCAUGU	128
hsa-miR-219-2-3p-4395501	AGAAUUGUGGCUGGACAUCUGU	129
hsa-miR-22#-002301	AGUUCUUCAGUGGCAAGCUUUA	130
hsa-miR-220b-4395317	CCACCACCGUGUCUGACACUU	131
hsa-miR-222#-002097	CUCAGUAGCCAGUGUAGAUCCU	132
hsa-miR-223-4395406	UGUCAGUUUGUCAAAUACCCCA	133
hsa-miR-23a-4373074	AUCACAUUGCCAGGGAUUUCC	134
hsa-miR-24-1#-002440	UGCCUACUGAGCUGAUAUCAGU	135
hsa-miR-25-4373071	CAUUGCACUUGUCUCGGUCUGA	136
hsa-miR-26a-2#-002115	CCUAUUCUUGAUUACUUGUUUC	137
hsa-miR-26b#-002444	CCUGUUCUCCAUUACUUGGCUC	138
hsa-miR-27a#-002445	AGGGCUUAGCUGCUUGUGAGCA	139
hsa-miR-27b-4373068	UUCACAGUGGCUAAGUUCUGC	140
hsa-miR-28-3p-4395557	CACUAGAUUGUGAGCUCCUGGA	141
hsa-miR-296-3p-4395212	GAGGGUUGGGUGGAGGCUCUCC	142
hsa-miR-296-5p-4373066	AGGGCCCCCCCUCAAUCCUGU	143
hsa-miR-29a#-002447	ACUGAUUUCUUUUGGUGUUCAG	144
hsa-miR-29a-4395223	UAGCACCAUCUGAAAUCGGUUA	145
hsa-miR-29c-4395171	UAGCACCAUUUGAAAUCGGUUA	146

TABLE 39-continued

Sequences of exemplary miRNAs.

miRNA	Sequences	SEQ ID NO
hsa-miR-302a-4378070	UAAGUGCUUCCAUGUUUUGGUGA	147
hsa-miR-302d-000535	UAAGUGCUUCCAUGUUUGAGUGU	148
hsa-miR-30a-3p-000416	CUUUCAGUCGGAUGUUUGCAGC	149
hsa-miR-30b-4373290	UGUAAACAUCCUACACUCAGCU	150
hsa-miR-30c-1#-002108	CUGGGAGAGGGUUGUUUACUCC	151
hsa-miR-30e-3p-000422	CUUUCAGUCGGAUGUUUACAGC	152
hsa-miR-31#-002113	UGCUAUGCCAACAUAUUGCCAU	153
hsa-miR-31-4395390	AGGCAAGAUGCUGGCAUAGCU	154
hsa-miR-320B-002844	AAAAGCUGGGUUGAGAGGGCAA	155
hsa-miR-324-5p-4373052	CGCAUCCCCUAGGGCAUUGGUGU	156
hsa-miR-326-4373050	CCUCUGGGCCCUUCCUCCAG	157
hsa-miR-328-4373049	CUGGCCCUCUCUGCCCUUCCGU	158
hsa-miR-330-5p-4395341	UCUCUGGGCCUGUGUCUUAGGC	159
hsa-miR-337-3p-002157	CUCCUAUAUGAUGCCUUUCUUC	160
hsa-miR-338-3p-4395363	UCCAGCAUCAGUGAUUUUGUUG	161
hsa-miR-339-5p-4395368	UCCCUGUCCUCCAGGAGCUCACG	162
hsa-miR-33b-4395196	GUGCAUUGCUGUUGCAUUGC	163
hsa-miR-340#-002259	UCCGUCUCAGUUACUUUAUAGC	164
hsa-miR-340-4395369	UUAUAAAGCAAUGAGACUGAUU	165
hsa-miR-345-4395297	GCUGACUCCUAGUCCAGGGCUC	166
hsa-miR-34a#-002316	CAAUCAGCAAGUAUACUGCCCU	167
hsa-miR-34a-4395168	UGGCAGUGUCUUAGCUGGUUGU	168
hsa-miR-34b-000427	UAGGCAGUGUCAUUAGCUGAUUG	169
hsa-miR-34c-5p-4373036	AGGCAGUGUAGUUAGCUGAUUGC	170
hsa-miR-362-5p-4378092	AAUCCUUGGAACCUAGGUGUGAGU	171
hsa-miR-363#-001283	CGGGUGGAUCACGAUGCAAUUU	172
hsa-miR-363-4378090	AAUUGCACGGUAUCCAUCUGUA	173
hsa-miR-365-4373194	UAAUGCCCCUAAAAAUCCUUAU	174
hsa-miR-367-4373034	AAUUGCACUUUAGCAAUGGUGA	175
hsa-miR-373-4378073	GAAGUGCUUCGAUUUUGGGGUGU	176
hsa-miR-374b#-002391	CUUAGCAGGUUGUAUUAUCAUU	177
hsa-miR-374b-4381045	AUAUAAUACAACCUGCUAAGUG	178
hsa-miR-376c-4395233	AACAUAGAGGAAAUUCCACGU	179
hsa-miR-378-000567	CUCCUGACUCCAGGUCCUGUGU	180
hsa-miR-380-5p-000570	UGGUUGACCAUAGAACAUGCGC	181
hsa-miR-381-4373020	UAUACAAGGGCAAGCUCUCUGU	182
hsa-miR-382-4373019	GAAGUUGUUCGUGGUGGAUUCG	183
hsa-miR-383-4373018	AGAUCAGAAGGUGAUUGUGGCU	184
hsa-miR-409-3p-002332	GAAUGUUGCUCGGUGAACCCCU	185
hsa-miR-411-4381013	UAGUAGACCGUAUAGCGUACG	186
hsa-miR-424#-002309	CAAAACGUGAGGCGCUGCUAU	187
hsa-miR-424-4373201	CAGCAGCAAUUCAUGUUUUGAA	188
hsa-miR-431-4395173	UGUCUUGCAGGCCGUCAUGCA	189
hsa-miR-432-001026	UCUUGGAGUAGGUCAUUGGGUGG	190
hsa-miR-448-4373206	UUGCAUAUGUAGGAUGUCCCAU	191
hsa-miR-449b-4381011	AGGCAGUGUAUUGUUAGCUGGC	192
hsa-miR-450a-4395414	UUUUGCGAUGUGUUCCUAAUAU	193
hsa-miR-454-4395434	UAGUGCAAUAUUGCUUAUAGGGU	194
hsa-miR-483-3p-002339	UCACUCCUCUCCUCCCGUCUU	195
hsa-miR-484-4381032	UCAGGCUCAGUCCCCUCCCGAU	196
hsa-miR-486-5p-4378096	UCCUGUACUGAGCUGCCCCGAG	197
hsa-miR-488-4395468	UUGAAAGGCUAUUUCUUGGUC	198
hsa-miR-489-4395469	GUGACAUCACAUAUACGGCAGC	199
hsa-miR-497-001043	CAGCAGCACACUGUGGUUUGU	200
hsa-miR-499-5p-4381047	UUAAGACUUGCAGUGAUGUUUAA	201
hsa-miR-500-001046	AUGCACCUGGGCAAGGAUUCUG	202
hsa-miR-511-4373236	GUGUCUUUUGCUCUGCAGUCA	203
hsa-miR-516-3p-001149	UGCUUCCUUUCAGAGGGU	204
hsa-miR-516b-4395172	AUCUGGAGGUAAGAAGCACUUU	205
hsa-miR-517#-001113	CCUCUAGAUGGAAGCACUGUCU	206
hsa-miR-518a-3p-4395508	GAAAGCGCUUCCCUUUGCUGGA	207
hsa-miR-518b-4373246	CAAAGCGCUCCCCUUUAGAGGU	208
hsa-miR-519a-4395526	AAAGUGCAUCCUUUUAGAGUGU	209
hsa-miR-520c-3p-002400	AAAGUGCUUCCUUUUAGAGGGU	210
hsa-miR-520D-3P-002743	AAAGUGCUUCUCUUUGGUGGGU	211
hsa-miR-520g-4373257	ACAAAGUGCUUCCCUUUAGAGUGU	212
hsa-miR-521-4373259	AACGCACUUCCCUUUAGAGUGU	213
hsa-miR-539-4378103	GGAGAAAUUAUCCUUGGUGUGU	214
hsa-miR-541-4395312	UGGUGGGCACAGAAUCUGGACU	215
hsa-miR-543-002376	AAACAUUCGCGGUGCACUUCUU	216
hsa-miR-545-4395378	UCAGCAAACAUUUAUUGUGUGC	217
hsa-miR-548b-5p-4395519	AAAAGUAAUUGUGGUUUUGGCC	218
hsa-miR-548c-5p-4395540	AAAAGUAAUUGCGGUUUUUGCC	219
hsa-miR-5481-002909	AAAAGUAAUUGCGGAUUUUGCC	220
hsa-miR-551b#-002346	GAAAUCAAGCGUGGGUGAGACC	221

TABLE 39-continued

Sequences of exemplary miRNAs.

miRNA	Sequences	SEQ ID NO
hsa-miR-552-001520	AACAGGUGACUGGUUAGACAA	222
hsa-miR-559-001527	UAAAGUAAAUAUGCACCAAAA	223
hsa-miR-566-001533	GGGCGCCUGUGAUCCCAAC	224
hsa-miR-571-001613	UGAGUUGGCCAUCUGAGUGAG	225
hsa-miR-574-3p-4395460	CACGCUCAUGCACACACCCACA	226
hsa-miR-577-002675	UAGAUAAAAUAUUGGUACCUG	227
hsa-miR-582-3p-4395510	UAACUGGUUGAACAACUGAACC	228
hsa-miR-589-001543	UCAGAACAAAUGCCGGUUCCCAGA	229
hsa-miR-590-3P-002677	UAAUUUUAUGUAUAAGCUAGU	230
hsa-miR-590-5p-4395176	GAGCUUAUUCAUAAAAGUGCAG	231
hsa-miR-592-001546	UUGUGUCAAUAUGCGAUGAUGU	232
hsa-miR-593-001547	AGGCACCAGCCAGGCAUUGCUCAGC	233
hsa-miR-597-4380960	UGUGUCACUCGAUGACCACUGU	234
hsa-miR-601-001558	UGGUCUAGGAUUGUUGGAGGAG	235
hsa-miR-604-001567	AGGCUGCGGAAUUCAGGAC	236
hsa-miR-608-001571	AGGGGUGGUGUUGGGACAGCUCCGU	237
hsa-miR-616-4395525	AGUCAUUGGAGGGUUUGAGCAG	238
hsa-miR-617-001591	AGACUUCCCAUUUGAAGGUGGC	239
hsa-miR-618-4380996	AAACUCUACUUGUCCUUCUGAGU	240
hsa-miR-622-001553	ACAGUCUGCUGAGGUUGGAGC	241
hsa-miR-625#-002432	GACUAUAGAACUUUCCCCCUCA	242
hsa-miR-626-001559	AGCUGUCUGAAAAUGUCUU	243
hsa-miR-628-3p-002434	UCUAGUAAGAGUGGCAGUCGA	244
hsa-miR-628-5p-4395544	AUGCUGACAUAUUUACUAGAGG	245
hsa-miR-629-001562	UGGGUUUACGUUGGGAGAACU	246
hsa-miR-630-001563	AGUAUUCUGUACCAGGGAAGGU	247
hsa-miR-635-001578	ACUUGGGCACUGAAACAAUGUCC	248
hsa-miR-638-001582	AGGGAUCGCGGGCGGGUGGCGGCCU	249
hsa-miR-639-001583	AUCGCUGCGGUUGCGAGCGCUGU	250
hsa-miR-641-001585	AAAGACAUAGGAUAGAGUCACCUC	251
hsa-miR-644-001596	AGUGUGGCUUUCUUAGAGC	252
hsa-miR-649-001602	AAACCUGUGUUGUUCAAGAGUC	253
hsa-miR-652-4395463	AAUGGCGCCACUAGGGUUGUG	254
hsa-miR-654-3p-4395350	UAUGUCUGCUGACCAUCACCUU	255
hsa-miR-659-001514	CUUGGUUCAGGGAGGGUCCCCA	256
hsa-miR-660-4380925	UACCCAUUGCAUAUCGGAGUUG	257
hsa-miR-661-001606	UGCCUGGGUCUCUGGCCUGCGCGU	258
hsa-miR-663B-002857	GGUGGCCCGGCCGUGCCUGAGG	259
hsa-miR-664-002897	UAUUCAUUUAUCCCCAGCCUACA	260
hsa-miR-671-3p-4395433	UCCGGUUCUCAGGGCUCCACC	261
hsa-miR-708-4395452	AAGGAGCUUACAAUCUAGCUGGG	262
hsa-miR-720-002895	UCUCGCUGGGGCCUCCA	263
hsa-miR-758-4395180	UUUGUGACCUGGUCCACUAACC	264
hsa-miR-767-5p-001993	UGCACCAUGGUUGUCUGAGCAUG	265
hsa-miR-769-5p-001998	UGAGACCUCUGGGUUCUGAGCU	266
hsa-miR-873-4395467	GCAGGAACUUGUGAGUCUCCU	267
hsa-miR-876-3p-4395336	UGGUGGUUUACAAAGUAAUUCA	268
hsa-miR-885-5p-4395407	UCCAUUACACUACCCUGCCUCU	269
hsa-miR-886-3p-4395305	CGCGGGUGCUUACUGACCCUU	270
hsa-miR-886-5p-4395304	CGGGUCGGAGUUAGCUCAAGCGG	271
hsa-miR-9#-002231	AUAAAGCUAGAUAACCGAAAGU	272
hsa-miR-920-002150	GGGGAGCUGUGGAAGCAGUA	273
hsa-miR-922-002152	GCAGCAGAGAAUAGGACUACGUC	274
hsa-miR-92a-1#-002137	AGGUUGGGAUCGGUUGCAAUGCU	275
hsa-miR-92a-4395169	UAUUGCACUUGUCCCGGCCUGU	276
hsa-miR-9-4373285	UCUUUGGUUAUCUAGCUGUAUGA	277
hsa-miR-98-4373009	UGAGGUAGUAAGUUGUAUUGUU	278
hsa-miR-99a#-002141	CAAGCUCGCUUCUAUGGGUCUG	279
hsa-miR-99b-4373007	CACCCGUAGAACCGACCUUGCG	280
mmu-let-7d#-001178	CUAUACGACCUGCUGCCUUUCU	281
rno-miR-29c#-001818	UGACCGAUUUCUCCUGGUGUUC	282
rno-miR-7#-001338	CAACAAAUCACAGUCUGCCAUA	283

As shown in the Examples discovered are miRNAs that are useful as diagnostic markers and therapeutic targets for the treatment and prevention of Parkinson's Disease and related disorders. As used herein, disorders related to Parkinson's Disease may include, but are not limited to, Alzheimer's, dementia, cognitive impairment, pre-symptomatic Parkinson's Disease, and Lewis Body disease.

miRNA or microRNA refer to 19-25 nucleotide (nt) non-coding RNAs derived from endogenous genes that act as post-transcriptional regulators of gene expression. They are processed from longer (ca 70-80 nt) hairpin-like precursors termed pre-miRNAs by the RNAse III enzyme Dicer. miRNAs assemble in ribonucleoprotein complexes termed miRNPs and recognise their target sites by antisense complementarity thereby mediating down-regulation of their target genes. Near-perfect or perfect complementarity between the miRNA and its target site results in target mRNA cleavage, whereas limited complementarity between

the miRNA and the target site results in translational inhibition of the target gene.

Compositions

In certain aspects, provided are pharmaceutical compositions. The pharmaceutical compositions may include an oligonucleotide that down-regulates the over-expression of at least one miRNA of SEQ ID NOs: 1-283. The oligonucleotide may be complementary to the nucleotide sequence of at least one of SEQ ID NOs: 1-283. The oligonucleotide may hybridize under stringent conditions to a nucleotide sequence of at least one of SEQ ID NOs: 1-283. The oligonucleotide may comprise any nucleic acid. "Nucleic acid" includes double- and single-stranded DNA of different lengths, as well as double- and single stranded RNA of different lengths, or synthetic variants thereof. Thus, the nucleic acid may be, for example, DNA, cDNA, RNA, sRNA, locked nucleotide acid (LNA), HNA, peptide nucleic acid (PNA), or any other variant hereof.

As used herein, "complementary" or "substantially complementary" refers to the hybridization or base pairing between nucleotides or nucleic acids, such as, for instance, between the two strands of a double stranded DNA molecule or between an oligonucleotide primer and a primer binding site on a single stranded nucleic acid to be sequenced or amplified. Complementary nucleotides are, generally, A and T (or A and U), or C and G. Two single stranded RNA or DNA molecules are said to be substantially complementary when the nucleotides of one strand, optimally aligned and with appropriate nucleotide insertions or deletions, pair with at least about 80% of the nucleotides of the other strand, usually at least about 90% to 95%, and more preferably from about 98 to 100%

The oligonucleotide may be at least about 10 nucleotides (nt), at least about 11 nt, at least about 12 nt, at least about 13 nt, at least about 14 nt, at least about 15 nt, at least about 16 nt, at least about 17 nt, at least about 18 nt, at least about 19 nt, or at least about 20 nt in length. The oligonucleotide may be less than about 100 nt, less than about 90 nt, less than about 80 nt, less than about 70 nt, less than about 60 nt, or less than about 50 nt in length. This may include ranges of about 10 nt to about 50 nt, about 12 nt to about 40 nt, or about 15 nt to about 30 nt in length.

The oligonucleotide may be capable of reducing expression of the miRNA by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, or at least about 60%. The oligonucleotide may be capable of reducing expression of the miRNA by less than about 99%, less than about 98%, less than about 95%, less than about 90%, less than about 85%, less than about 80%, or less than about 75%. This may include ranges of about 10% to about 99%, about 20% to about 98%, about 30% to about 90%, or about 40% to about 80%.

The oligonucleotide may be chemically modified. Chemical modifications may include addition of an imaging agent or reporter molecule. As used herein, an "imaging agent" or "reporter molecule" is any entity which enhances visualization or detection of the oligonucleotide. Any type of detectable reporter molecule/imaging agent can be used in the methods disclosed herein. Such detectable molecules are known in the art and include, for example, magnetic beads, fluorophores, radionuclides, nuclear stains (e.g., DAPI). For example, an imaging agent can include a compound that comprises an unstable isotope (i.e., a radionuclide) or a fluorescent moiety, such as Cy-5, Alexa 647, Alexa 555, Alexa 488, fluorescein, rhodamine, and the like. Suitable radionuclides include both alpha- and beta-emitters. In some embodiments, the targeting vehicle is labeled. In other embodiments, suitable radioactive moieties include labeled polynucleotides and polypeptides which can be coupled to the targeting vehicle.

In some embodiments, the imaging agent comprises a radionuclide such as, for example, a radionuclide that emits low-energy electrons (e.g., those that emit photons with energies as low as 20 keV). Such nuclides can irradiate the cell to which they are delivered without irradiating surrounding cells or tissues. Non-limiting examples of radionuclides that are can be delivered to cells include ^{137}Cs, ^{103}Pd, ^{111}In, ^{125}I, ^{211}At, ^{212}Bi and ^{213}Bi, among others known in the art. Further imaging agents suitable for delivery to a cell in accordance with some embodiments include paramagnetic species for use in MRI imaging, echogenic entities for use in ultrasound imaging, fluorescent entities for use in fluorescence imaging (including quantum dots), and light-active entities for use in optical imaging. A suitable species for MRI imaging is a gadolinium complex of diethylenetriamine pentacetic acid (DTPA). For positron emission tomography (PET), ^{18}F or ^{11}C may be delivered.

Methods

In further aspects, the disclosure relates to methods of diagnosing Parkinson's Disease (PD) in a subject. The methods may include detecting the level of expression of at least one miRNA of SEQ ID NOs: 1-283 in a biological sample from the subject, and comparing the level of expression in the sample to the level of expression in a reference. An increased or decreased level of expression in the sample compared to the level of expression in the reference may identify the subject as having PD or who is at risk of developing PD.

Various detection methods that can be employed for the methods described herein, and the present invention includes all the mentioned methods, but is not limited to any of these. Detection methods may include use of a probe. A probe is a specific sequence of a nucleic acid used to detect nucleic acids by hybridization. A probe may be labelled, tagged or immobilized or otherwise modified according to the requirements of the detection method chosen. A label or a tag is an entity making it possible to identify a compound to which it is associated. It is within the scope of the present invention to employ probes that are labelled or tagged by any means known in the art such as but not limited to: radioactive labelling, fluorescent labelling and enzymatic labelling. Furthermore the probe, labeled or not, may be immobilized to facilitate detection according to the detection method of choice and this may be accomplished according to the preferred method of the particular detection method. Detection methods may also include in situ hybridization, PCR, microarrays, Northern blot analysis, and affinity matrices.

In some embodiments, RT-PCR may be used as the detection method. In some embodiments, the detection method may include quantitative real-time RT-PCR, for example, the TaqMan® MicroRNA assay (Applied Biosystems) may be used for detection of expression of the miRNAs described herein.

In some embodiments, a kit may be provided with reagents to measure at least one of the miRNAs. In some embodiments, a kit may be provided to measure a miRNA signature. By way of non-limiting example, the kit may include reagents to measure a miRNA signature where the miRNA signature includes at least one of SEQ ID NOs: 204, 110, 192, 200, 244, 21, 134, 144, 198, 234, 143, 261, 255, and 179 (miR-516-3p, miR-191#, miR-449b, miR-497, miR-628-3p, miR-213, miR-23a, miR-29a#, miR-488, miR-597, miR-296-5p, miR-671-3p, miR-654-3p, and miR-99a#)

or a combination thereof and in some embodiments includes all 14. An embodiment of the kit may include reagents to measure a miRNA signature where the miRNA signature includes at least one of SEQ ID NOs: 1-13, (miR-590-3p, miR-213, miR-9#, miR-191#, miR-497, miR-664, miR-99a#, miR-1183, miR-340#, miR-628-3p, miR-7#, miR-29a#, miR-142-3p) or combinations thereof and in some embodiments includes all 13. An embodiment of the kit may include reagents to measure a miRNA signature where the miRNA signature includes at least one of SEQ ID NOs: 14-21 (miR-590-3p, miR-664, miR-519a, miR-340#, miR-720, miR-142-3p, miR-185, and miR-213) or combinations thereof an in some embodiments includes all 8. An embodiment of the kit may include reagents to measure a miRNA signature where the miRNA signature includes at least one of SEQ ID NOs: 22-27 (miR-664, miR-1285, miR-1183, miR-143, miR-519a, miR-603) or combinations thereof an in some embodiments includes all 6. An embodiment of the kit may include reagents to measure a miRNA signature where the miRNA signature includes at least one of SEQ ID NOs: 28-34 (miR-590-3p, miR-213, miR-409-3p, miR-500, miR-7, miR-206, and miR-629) or combinations thereof an in some embodiments includes all 7. Additional combinations for the kit for measuring a miRNA signature are also possible.

In some embodiments, the expression level of one or more miRNAs of SEQ ID NOS 1-283 may be compared to a reference expression level using statistical analysis with a computer to implement the statistical analysis. In some embodiments Support Vector Machine Recursive Feature Selection (SVM-RFE) and SVM classification analysis from JMP Genomics (SAS Institute) is used to compare the miRNA expression levels. In some embodiments, the data for the array assays will be first analyzed using RQ manager 1.2 software (Applied Biosystems) to obtain raw expression levels of all the miRNAs in each sample, represented by C^T. In some embodiments, the miRNA expression profiles of ILBD, PD, and PDDnoAD patients may be compared to age-matched normal controls in the CSF or SNs. The miRNA profiles of ILBD, PD, and PDDnoAD patients may be compared to each other. Changes in the levels of miRNA expression in each pair will be evaluated by the DDCt or $\Delta(\Delta C^T)$. In some embodiments, StatMiner software (Integromics) may be used for bioinformatic and statistical analysis.

The subject may be any mammal. Mammals include including humans, mice, rats, rabbits, cats, and dogs. The subject is preferably human. The subject may be predisposed for a disease or suffering from a disease.

A sample may be a small part of a subject, representative of the whole, and may be constituted by a biopsy or a body fluid sample. Biopsies are small pieces of tissue and may be fresh, frozen or fixed, such as formalin-fixed and paraffin embedded (FFPE). Body fluid samples may be blood, plasma, serum, urine, sputum, cerebrospinal fluid, milk, or ductal fluid samples and may likewise be fresh, frozen or fixed. Suitably, the sample comprises blood. Samples may be removed surgically, by extraction, i.e. by hypodermic or other types of needles, by microdissection, or laser capture.

The reference may be any suitable control sample known in the art, such as, for example, a sample from a normal, healthy subject. The reference may be a sample from the same subject prior to demonstration of disease symptoms or prior to diagnosis with Parkinson's Disease. The reference may be a "standardized" sample, such as a sample comprising material or data from several samples, preferably also from several individuals. A standardized sample may comprise either normal or diseased sample material or data.

Before analyzing the sample, it may be desirable to perform one or more sample preparation operations upon the sample. Typically, these sample preparation operations will include such manipulations as concentration, suspension, extraction of intracellular material, e.g., nucleic acids from tissue/whole cell samples and the like, amplification of nucleic acids, fragmentation, transcription, labeling and/or extension reactions. Nucleic acids, especially RNA and specifically miRNA can be isolated using any techniques known in the art. There are two main methods for isolating RNA: phenol-based extraction and silica matrix or glass fiber filter (GFF)-based binding. Phenol-based reagents contain a combination of denaturants and RNase inhibitors for cell and tissue disruption and subsequent separation of RNA from contaminants. Phenol-based isolation procedures can recover RNA species in the 10-200-nucleotide range e.g., miRNAs, 5S rRNA, 5.8S rRNA, and U1 snRNA. If a sample of "total" RNA was purified by the popular silica matrix column or GFF procedure, it may be depleted in small RNAs. Extraction procedures such as those using Trizol or TriReagent, however will purify all RNAs, large and small, and are the recommended methods for isolating total RNA from biological samples that will contain miRNAs/siRNAs. Any method required for the processing of a sample prior to detection by any of the herein mentioned methods falls within the scope of the present invention. These methods are typically well known by a person skilled in the art.

Other aspects of the disclosure provide methods for treating, preventing, or reducing the risk of PD associated with aberrant expression of a miRNA in a cell, tissue, or animal. The methods may include contacting the cell, tissue, or animal with a pharmaceutical composition as detailed above. Aberrant expression includes up-regulation and down-regulation of the miRNA. In some embodiments, miRNA is up-regulated.

"Administration" or "administering," as used herein, refers to providing, contacting, and/or delivery of a compound or compounds by any appropriate route to achieve the desired effect. Administration may include, but is not limited to, oral, sublingual, parenteral (e.g., intravenous, subcutaneous, intracutaneous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional or intracranial injection), transdermal, topical, buccal, rectal, vaginal, nasal, ophthalmic, via inhalation, and implants.

"Contacting," as used herein as in "contacting a cell," refers to contacting a cell directly or indirectly in vitro, ex vivo, or in vivo (i.e. within a subject, such as a mammal). Contacting a cell, which also includes "reacting" a cell, can occur as a result of administration to a subject. Contacting encompasses administration to a cell, tissue, mammal, subject, patient, or human. Further, contacting a cell includes adding an agent to a cell culture. Other suitable methods may include introducing or administering an agent to a cell, tissue, mammal, subject, or patient using appropriate procedures and routes of administration as defined herein.

As used herein, the term "treat" or "treating" a subject having a disorder refers to administering a regimen to the subject, such that at least one symptom of the disorder is cured, healed, alleviated, relieved, altered, remedied, ameliorated, or improved. Treating includes administering an amount effective to alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disorder or the symptoms of the disorder. The treatment may inhibit deterioration or worsening of a symptom of a disorder.

The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including but not limited to") unless otherwise noted. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to illustrate aspects and embodiments of the disclosure and does not limit the scope of the claims.

EXAMPLES

Example 1

Putamen miRNAs are Involved in the Pathogenesis of PD and are Novel Therapeutic Targets for Treatment of PD

Among the differentially expressed miRNAs in the putamen, we identified 51 miRNAs that are dysregulated among ILBD, PD and PDD, and normal controls (Tables 3-9; FIG. **1**); 59 miRNAs that are dysregulated in Stages 2, 3, and 4 of Lewy Body diseases when compared to normal controls (Tables 10-16; FIG. **2**).

TABLE 3

miRNAs Differentially Expressed in Putamen among Different Diagnostic Groups ($p < 0.05$; at least 2 fold change) (51 in total)

Diagnosis	Control	ILBD	PD	PDDnoAD
Control		27 (11, 16)	16 (7, 9)	11 (3, 8)
ILBD	27 (11, 16)		14 (8, 6)	18 (10, 8)
PD	16 (7, 9)	14 (8, 6)		12 (6, 6)
PDDnoAD	11 (3, 8)	18 (10, 8)	12 (6, 6)	

*Numbers in parentheses are numbers of (upregulated, downregulated) miRNAs.

TABLE 4

miRNAs differentially expressed in ILBD compared to normal controls (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (ILBD/Ctl)
hsa-miR-1224-3P-002752	0.007	10.69
hsa-miR-767-5p-001993	0.008	5.31
hsa-miR-431-4395173	0.009	4.25
mmu-let-7d#-001178	0.013	3.46
hsa-miR-183-4395380	0.000	3.37
hsa-miR-873-4395467	0.015	2.68
hsa-miR-33b-4395196	0.040	2.55
hsa-miR-516b-4395172	0.015	2.53
hsa-miR-127-5p-4395340	0.030	2.32
hsa-miR-489-4395469	0.001	2.08
hsa-miR-1270-002807	0.029	2.06
hsa-miR-34b-000427	0.008	0.20
hsa-miR-26a-2#-002115	0.002	0.22
hsa-miR-638-001582	0.000	0.22
hsa-miR-1290-002863	0.002	0.23
hsa-miR-302d-000535	0.016	0.23
hsa-miR-1248-002870	0.020	0.24
hsa-miR-922-002152	0.024	0.26
hsa-miR-30c-1#-002108	0.000	0.30
hsa-miR-92a-1#-002137	0.002	0.31
hsa-miR-497-001043	0.000	0.34

TABLE 4-continued

miRNAs differentially expressed in ILBD compared to normal controls (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (ILBD/Ctl)
hsa-miR-1291-002838	0.005	0.36
hsa-miR-1244-002791	0.009	0.40
hsa-miR-635-001578	0.009	0.43
hsa-miR-601-001558	0.009	0.44
hsa-miR-1226#-002758	0.043	0.47
hsa-miR-106b#-002380	0.002	0.47

TABLE 5

miRNAs differentially expressed in PD compared to normal controls (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (PD/Ctl)
hsa-miR-566-001533	0.01	15.96
hsa-miR-767-5p-001993	0.01	7.39
hsa-miR-1-4395333	0.01	2.94
hsa-miR-33b-4395196	0.03	2.88
hsa-miR-217-4395448	0.01	2.17
hsa-miR-424-4373201	0.04	2.17
hsa-miR-876-3p-4395336	0.02	2.12
hsa-miR-516-3p-001149	0.05	0.11
hsa-miR-644-001596	0.02	0.15
dme-miR-7-000268	0.05	0.27
hsa-miR-30c-1#-002108	0.01	0.38
hsa-miR-720-002895	0.04	0.39
hsa-miR-106b#-002380	0.00	0.42
hsa-miR-551b#-002346	0.02	0.46
hsa-miR-125b-2#-002158	0.02	0.48
hsa-miR-1256-002850	0.01	0.48

TABLE 6

miRNAs differentially expressed in PDD compared to normal controls (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (PDD/Ctl)
hsa-miR-518a-3p-4395508	0.011	2.910
hsa-miR-520g-4373257	0.045	2.891
hsa-miR-337-3p-002157	0.015	2.851
hsa-miR-516-3p-001149	0.042	0.090
hsa-miR-644-001596	0.042	0.183
hsa-miR-922-002152	0.013	0.286
hsa-miR-193a-3p-4395361	0.017	0.300
hsa-miR-92a-1#-002137	0.038	0.371
hsa-miR-30c-1#-002108	0.004	0.373
hsa-miR-1291-002838	0.017	0.415
hsa-miR-15a-4373123	0.039	0.472

TABLE 7

miRNAs differentially expressed in PD compared to ILBD (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (PD/ILBD)
hsa-miR-302d-000535	0.004	6.208
hsa-miR-23a-4373074	0.037	4.953
hsa-miR-1290-002863	0.018	3.974
hsa-miR-26a-2#-002115	0.025	3.090
hsa-miR-638-001582	0.005	3.028
hsa-miR-886-3p-4395305	0.049	2.740
hsa-miR-548c-5p-4395540	0.040	2.241
hsa-miR-92a-1#-002137	0.010	2.141
hsa-miR-1224-3P-002752	0.049	0.273
hsa-miR-122-4395356	0.019	0.308
hsa-miR-302a-4378070	0.009	0.357

TABLE 7-continued

miRNAs differentially expressed in PD compared to ILBD (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (PD/ILBD)
hsa-miR-424#-002309	0.032	0.380
hsa-miR-486-5p-4378096	0.010	0.409
hsa-miR-541-4395312	0.004	0.455

TABLE 8

miRNAs differentially expressed in PDD compared to ILBD (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	fold change (PDD/ILBD)
hsa-miR-302d-000535	0.008	5.830
hsa-miR-26a-2#-002115	0.002	4.415
hsa-miR-630-001563	0.046	3.232
hsa-miR-659-001514	0.030	3.229
hsa-miR-641-001585	0.006	2.826
hsa-miR-638-001582	0.011	2.586
hsa-miR-125b-2#-002158	0.044	2.458
hsa-miR-1255B-002801	0.010	2.387
hsa-miR-337-3p-002157	0.048	2.190
hsa-miR-380-5p-000570	0.009	2.058
hsa-miR-202-4395474	0.005	0.260
hsa-miR-873-4395467	0.001	0.279
hsa-miR-767-5p-001993	0.040	0.298
hsa-miR-431-4395173	0.010	0.317
hsa-miR-1224-3P-002752	0.050	0.371
hsa-miR-24-1#-002440	0.034	0.408
hsa-miR-15a-4373123	0.002	0.455
hsa-miR-339-5p-4395368	0.001	0.494

TABLE 9

miRNAs differentially expressed in PDD compared to PD (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold Change (PDD/PD)
dme-miR-7-000268	0.031	4.086
hsa-miR-135b#-002159	0.049	2.608
hsa-miR-641-001585	0.003	2.553
hsa-miR-149#-002164	0.006	2.490
hsa-miR-154#-000478	0.007	2.291
hsa-miR-521-4373259	0.028	2.192
hsa-miR-566-001533	0.035	0.115
hsa-miR-767-5p-001993	0.025	0.214
hsa-miR-202-4395474	0.008	0.321
hsa-miR-548b-5p-4395519	0.025	0.356
hsa-miR-217-4395448	0.011	0.414
hsa-miR-326-4373050	0.042	0.463

TABLE 10

miRNAs Differentially Expressed in Putamen among Different Stage Groups by the Unified Staging System for LBD ($p < 0.05$; at least 2 fold change). (59 in total)

Stages	0	2	3	4
0		29 (9, 20)	24 (11, 13)	10 (3/7)
2	29 (9, 20)		9 (4, 5)	13 (7, 6)
3	24 (11, 13)	9 (4, 5)		7 (3, 4)
4	10 (3/7)	13 (7, 6)	7 (3, 4)	

*Numbers in parentheses are numbers of (upregulated, downregulated) miRNAs.

TABLE 11

miRNAs differentially expressed in the putamen of Stage II compared to controls (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (Stage2/0)
hsa-miR-1224-3P-002752	0.016	8.494
hsa-miR-767-5p-001993	0.027	5.601
mmu-let-7d#-001178	0.008	3.631
hsa-miR-33b-4395196	0.035	2.762
hsa-miR-516b-4395172	0.033	2.435
hsa-miR-183-4395380	0.006	2.427
hsa-miR-1-4395333	0.031	2.393
hsa-miR-127-5p-4395340	0.048	2.089
hsa-miR-489-4395469	0.001	2.031
hsa-miR-644-001596	0.015	0.157
hsa-miR-1290-002863	0.003	0.250
hsa-miR-1248-002870	0.015	0.254
hsa-miR-638-001582	0.001	0.269
hsa-miR-639-001583	0.017	0.274
hsa-miR-1303-002792	0.025	0.284
hsa-miR-30c-1#-002108	0.000	0.310
hsa-miR-378-000567	0.041	0.318
hsa-miR-26a-2#-002115	0.036	0.326
hsa-miR-1291-002838	0.002	0.328
hsa-miR-616-4395525	0.015	0.342
hsa-miR-922-002152	0.028	0.346
hsa-miR-1244-002791	0.000	0.358
hsa-miR-548c-5p-4395540	0.037	0.366
hsa-miR-92a-1#-002137	0.015	0.385
hsa-miR-497-001043	0.000	0.392
hsa-miR-601-001558	0.012	0.399
hsa-miR-720-002895	0.046	0.430
hsa-miR-1260-002896	0.004	0.452
hsa-miR-635-001578	0.041	0.495

TABLE 12

miRNAs differentially expressed in the putamen of Stage III compared to controls (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (Stage 3/0)
hsa-miR-566-001533	0.037	13.485
hsa-miR-1224-3P-002752	0.016	10.196
hsa-miR-98-4373009	0.046	4.805
hsa-miR-767-5p-001993	0.006	3.802
hsa-miR-1-4395333	0.039	3.115
hsa-miR-516b-4395172	0.018	2.728
hsa-miR-33b-4395196	0.049	2.448
hsa-miR-183-4395380	0.017	2.382
hsa-miR-424-4373201	0.017	2.288
hsa-miR-127-5p-4395340	0.033	2.144
hsa-miR-1270-002807	0.049	2.080
hsa-miR-34b-000427	0.031	0.231
hsa-miR-922-002152	0.037	0.286
hsa-miR-30c-1#-002108	0.001	0.323
hsa-miR-106b#-002380	0.000	0.353
hsa-miR-199a-5p-4373272	0.047	0.357
hsa-miR-520D-3P-002743	0.005	0.370
hsa-miR-100#-002142	0.000	0.400
hsa-miR-638-001582	0.022	0.401
hsa-miR-1226#-002758	0.023	0.408
hsa-miR-92a-1#-002137	0.039	0.411
hsa-miR-374b#-002391	0.005	0.436
hsa-miR-497-001043	0.006	0.460
hsa-miR-1260-002896	0.009	0.463

TABLE 13

miRNAs differentially expressed in the putamen of Stage IV compared to controls (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (Stage 4/0)
hsa-miR-518a-3p-4395508	0.027	2.605
hsa-miR-1269-002789	0.043	2.424
hsa-miR-876-3p-4395336	0.003	2.310
hsa-miR-516-3p-001149	0.025	0.095
hsa-miR-644-001596	0.038	0.192
hsa-miR-639-001583	0.022	0.257
hsa-miR-193a-3p-4395361	0.029	0.286
hsa-miR-30c-1#-002108	0.016	0.412
hsa-miR-635-001578	0.033	0.461
hsa-miR-511-4373236	0.014	0.497

TABLE 14

miRNAs differentially expressed in the putamen of Stage III compared to Stage II (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (Stage 3/2)
hsa-miR-616-4395525	0.029	2.383
hsa-miR-363#-001283	0.036	3.944
hsa-miR-604-001567	0.046	2.567
hsa-miR-639-001583	0.004	4.937
hsa-miR-199a-5p-4373272	0.037	0.287
hsa-let-7f-1#-002417	0.018	0.161
hsa-miR-1201-002781	0.035	0.371
hsa-miR-1301-002827	0.022	0.441
hsa-miR-920-002150	0.040	0.372

TABLE 15

miRNAs differentially expressed in the putamen of Stage IV compared to Stage II (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (Stage 4/2)
hsa-miR-1290-002863	0.005	3.942
hsa-miR-1248-002870	0.041	2.939
hsa-miR-638-001582	0.005	2.776
hsa-miR-1303-002792	0.036	2.440
hsa-miR-296-3p-4395212	0.031	2.412
hsa-miR-1255B-002801	0.004	2.314
hsa-miR-378-000567	0.031	2.149
hsa-let-7f-1#-002417	0.008	0.136
hsa-miR-1224-3P-002752	0.014	0.210
hsa-miR-571-001613	0.041	0.224
mmu-let-7d#-001178	0.037	0.386
hsa-miR-1227-002769	0.005	0.486
hsa-miR-511-4373236	0.011	0.497

TABLE 16

miRNAs differentially expressed in the putamen of Stage IV compared to Stage III (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (Stage 4/3)
hsa-miR-211-4373088	0.029	50.755
hsa-miR-876-3p-4395336	0.003	2.479
hsa-miR-100#-002142	0.005	2.208
hsa-miR-1224-3P-002752	0.008	0.175
hsa-miR-639-001583	0.006	0.190
hsa-miR-363#-001283	0.040	0.248
hsa-miR-873-4395467	0.019	0.434

We also identified expressions of 29 miRNAs are correlated with the global Lewy-type asynucleinopathy (LTS) scores; 32 miRNAs are correlated with the degree of depigmentation of the neurons in Substantia Nigra; 33 miRNAs are correlated with the worsening of the motor functions, Unified PD Rating System (UPDRS) (Table 17-20).

TABLE 17

Disease-correlated miRNAs in the Putamen (p < 0.05)

	By LTS Score*	By SN depigmentation score	By UPDRS**
Positively correlated	15	20	21
Negatively correlated	14	12	16

*LTS score: global Lewy-type α-synucleinopathy (LTS) scores.

**UPDRS: Unified PD Rating Scale.

TABLE 18

miRNAs whose expression levels are correlated with Lewy-type a-synucleinopathy (LTS) scores (p < 0.05)

miRNAs	r
hsa-miR-132-4373143	0.505
hsa-miR-212-4373087	0.453
hsa-miR-383-4373018	0.449
hsa-miR-885-5p-4395407	0.425
hsa-miR-132#-002132	0.406
hsa-miR-608-001571	0.401
hsa-miR-183#-002270	0.391
hsa-miR-587-001540	0.375
hsa-miR-1269-002789	0.375
hsa-miR-629-001562	0.370
hsa-let-7c-4373167	0.350
hsa-miR-559-001527	0.349
hsa-miR-129-3p-4373297	0.345
hsa-miR-130b#-002114	0.344
hsa-miR-125a-5p-4395309	0.322
hsa-miR-574-3p-4395460	−0.317
hsa-miR-374a-4373028	−0.320
hsa-miR-720-002895	−0.322
hsa-miR-1275-002840	−0.323
hsa-miR-142-5p-4395359	−0.330
hsa-miR-124-4373295	−0.330
hsa-miR-26b#-002444	−0.331
hsa-miR-1226#-002758	−0.350
hsa-miR-374b#-002391	−0.350
hsa-miR-193a-3p-4395361	−0.364
hsa-miR-590-5p-4395176	−0.379
hsa-miR-660-4380925	−0.388
hsa-miR-339-5p-4395368	−0.458
hsa-miR-106b#-002380	−0.473

TABLE 19

miRNAs whose expression levels are correlated with SN depigmentation scores (p < 0.05)

miRNAs	r
hsa-miR-132-4373143	0.548
hsa-miR-212-4373087	0.444
hsa-miR-1269-002789	0.410
hsa-miR-455-5p-4378098	0.377
hsa-miR-500-4395539	0.376
hsa-miR-139-3p-4395424	0.371
hsa-miR-183#-002270	0.366
hsa-miR-518b-4373246	0.361
hsa-miR-455-3p-4395355	0.348
hsa-miR-629-001562	0.341
hsa-miR-132#-002132	0.340
hsa-miR-23a-4373074	0.337
hsa-miR-335-4373045	0.320

TABLE 19-continued

miRNAs whose expression levels are correlated with SN depigmentation scores ($p < 0.05$)	
miRNAs	r
hsa-miR-580-001621	0.315
hsa-miR-383-4373018	0.312
hsa-miR-608-001571	0.312
hsa-miR-548l-002909	0.311
hsa-miR-505#-002087	0.299
hsa-let-7c-4373167	0.297
hsa-miR-129-3p-4373297	0.291
hsa-miR-17-4395419	−0.314
hsa-miR-503-4373228	−0.315
hsa-miR-193a-3p-435361	−0.322
hsa-miR-339-5p-4395368	−0.327
hsa-miR-140-5p-4373374	−0.327
hsa-miR-574-3p-4395460	−0.347
hsa-miR-302a-4378070	−0.361
hsa-miR-10b#-002315	−0.366
hsa-miR-93-4373302	−0.374
hsa-miR-590-5p-4395176	−0.419
hsa-miR-106b#-002380	−0.461
hsa-miR-124-4373295	−0.500

TABLE 20

miRNAs whose expression levels are correlated with UPDRS ($p < 0.05$)	
miRNAs	r
hsa-miR-198-4395384	0.582
hsa-miR-886-3p-4395305	0.528
hsa-miR-450a-4395414	0.525
hsa-miR-593-001547	0.523
hsa-miR-920-002150	0.518
hsa-miR-521-4373259	0.507
hsa-miR-629-4395547	0.501
hsa-miR-517#-001113	0.469
hsa-miR-520c-3p-002400	0.461
hsa-miR-125b-2#-002158	0.461
hsa-miR-27a#-002445	0.456
hsa-miR-559-001527	0.447
hsa-miR-589-001543	0.442
hsa-miR-886-5p-4395304	0.430
hsa-miR-1282-002803	0.430
hsa-miR-1270-002807	0.423
hsa-miR-99a#-002141	0.422
hsa-miR-181a-2#-002317	0.422
hsa-miR-608-001571	0.380
hsa-miR-211-4373088	0.378
hsa-miR-500-001046	0.376
hsa-miR-758-4395180	−0.408
hsa-miR-144-002676	−0.415
hsa-miR-138-4395395	−0.415
hsa-miR-92a-1#-002137	−0.422
hsa-miR-411-4381013	−0.425
hsa-miR-448-4373206	−0.427
hsa-miR-324-5p-4373052	−0.432
hsa-miR-203-4373095	−0.439
hsa-miR-107-4373154	−0.440
hsa-miR-488-4395468	−0.462
hsa-miR-137-4373301	−0.469
hsa-miR-148a-4373130	−0.475
hsa-miR-296-5p-4373066	−0.477
hsa-miR-218-4373081	−0.479
hsa-miR-153-4373305	−0.507
hsa-miR-552-001520	−0.521

These miRNAs may be involved in the pathological changes in the putamen, contributing to the pathogenesis of Lewy body diseases, including PD; and therefore, they may be new therapeutic targets for treatment of PD at different stages of the diseases.

Example 2

CSF miRNAs as Diagnostic Biomarkers for Presymptomatic and Early PD, and Cognitive Impairment in PD

Among the differentially expressed miRNAs in the CSF, we identified 80 miRNAs that are differentially expressed in ILBD, PD and PDD, when compared to normal controls (Tables 21-27; FIG. **3**); and 87 miRNAs that are differentially expression in Stages 2, 3, and 4 of Lewy Body diseases when compared to normal controls (Table 28-34; FIG. **4**).

TABLE 21

miRNAs Differentially Expressed in CSF Among Different Diagnostic Groups ($p < 0.05$; at least 2 fold change). (80 in total)				
Diagnosis	Control	ILBD	PD	PDDnoAD
Control		35 (25, 10)	27 (15, 12)	15 (13, 2)
ILBD	35 (25, 10)		11 (5, 6)	14 (8, 6)
PD	27 (15, 12)	11 (5, 6)		20 (8, 12)
PDDnoAD	15 (13, 2)	14 (8, 6)	20 (8, 12)	

*Numbers in parentheses are numbers of (upregulated, downregulated) miRNAs.

TABLE 22

CSF miRNAs differentially expressed in ILBD compared to control (corrected p value < 0.05, fold change > 2 folds)		
miRNAs	p-value	Fold Change (ILBD/ctl)
hsa-miR-497-001043	0.008	5.645
hsa-miR-126#-000451	0.026	5.413
hsa-miR-9#-002231	0.005	5.231
hsa-miR-1300-002902	0.023	5.129
hsa-miR-143-4395360	0.007	4.804
hsa-miR-374b-4381045	0.027	4.747
hsa-miR-660-4380925	0.005	4.465
hsa-miR-432-001026	0.046	4.313
hsa-miR-31#-002113	0.012	3.647
hsa-miR-324-5p-4373052	0.007	3.367
hsa-miR-99a#-002141	0.024	3.323
hsa-miR-628-3p-002434	0.002	3.318
hsa-miR-652-4395463	0.035	3.011
hsa-miR-1271-002779	0.039	2.775
hsa-miR-26b#-002444	0.016	2.706
hsa-miR-195-4373105	0.000	2.680
hsa-miR-340-4395369	0.031	2.568
hsa-miR-213-000516	0.032	2.524
hsa-miR-29a-4395223	0.003	2.483
hsa-miR-449b-4381011	0.045	2.348
hsa-miR-708-4395452	0.021	2.292
hsa-miR-29c-4395171	0.006	2.248
hsa-miR-218-4373081	0.016	2.223
hsa-miR-488-001106	0.014	2.155
hsa-miR-30e-3p-000422	0.035	2.154
hsa-miR-516-3p-001149	0.040	0.068
hsa-miR-296-5p-4373066	0.048	0.252
hsa-miR-671-3p-4395433	0.021	0.274
hsa-miR-145-4395389	0.016	0.289
hsa-miR-597-4380960	0.012	0.309
hsa-miR-328-4373049	0.025	0.362
hsa-miR-197-4373102	0.039	0.382
hsa-miR-92a-4395169	0.019	0.405
hsa-miR-484-4381032	0.023	0.432
hsa-miR-700-002895	0.044	0.449

TABLE 23

CSF miRNAs differentialiy expressed in PD compared to control (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold Change (PD/ctl)
hsa-miR-664-002897	0.001	18.334
hsa-miR-590-3P-002677	0.000	5.568
hsa-miR-577-002675	0.033	4.923
hsa-miR-374b-4381045	0.032	4.850
hsa-miR-9#-002231	0.006	4.755
hsa-miR-213-000516	0.001	4.217
rno-miR-7#-001338	0.044	3.712
hsa-miR-340#-002259	0.033	3.561
hsa-miR-497-001043	0.050	3.504
hsa-miR-454-4395434	0.013	3.093
hsa-miR-99a#-002141	0.049	3.050
hsa-miR-191#-002678	0.005	2.907
hsa-miR-1183-002841	0.038	2.387
hsa-miR-29a#-002447	0.030	2.243
hsa-miR-148b#-002160	0.014	2.137
hsa-miR-142-3p-4373136	0.029	0.260
hsa-miR-519a-4395526	0.016	0.318
hsa-miR-511-4373236	0.043	0.319
hsa-miR-486-5p-4378096	0.012	0.428
hsa-miR-92a-4395169	0.046	0.435
hsa-miR-381-4373020	0.037	0.435
hsa-miR-545-4395378	0.010	0.439
hsa-miR-196b-4395326	0.007	0.458
hsa-miR-10b-4395329	0.007	0.463
hsa-miR-98-4373009	0.006	0.465
hsa-miR-18a-4395533	0.003	0.470
hsa-miR-654-3p-4395350	0.008	0.473

TABLE 24

CSF miRNAs differentially expressed in PDDnoAD compared to control (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold Change (PDDnoAD/ctl)
hsa-miR-1300-002902	0.001	10.044
hsa-miR-664-002897	0.040	6.381
hsa-miR-374b-4381045	0.011	5.426
hsa-miR-1298-002861	0.033	4.569
hsa-miR-135b-4395372	0.003	3.592
hsa-miR-363-4378090	0.002	3.357
hsa-miR-660-4380925	0.032	3.189
hsa-miR-9#-002231	0.029	2.793
hsa-miR-362-5p-4378092	0.033	2.287
hsa-miR-29a-4395223	0.005	2.209
hsa-miR-1264-002799	0.028	2.090
hsa-miR-29a#-002447	0.049	2.073
hsa-miR-29c-4395171	0.003	2.043
hsa-miR-146b-5p-4373178	0.010	0.430
hsa-miR-518a-3p-4395508	0.020	0.372

TABLE 25

CSF miRNAs differentially expressed in PD compared to ILBD (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold Change (PD/ILBD)
hsa-miR-664-002897	0.028	4.750
hsa-miR-720-002895	0.006	3.384
hsa-miR-590-3P-002677	0.028	2.431
hsa-miR-625#-002432	0.033	2.096
hsa-miR-1183-002841	0.032	2.087
hsa-miR-143-4395360	0.026	0.315
hsa-miR-519a-4395526	0.005	0.334
hsa-miR-130a-4373145	0.025	0.414
hsa-miR-130b-4373144	0.037	0.422
hsa-miR-500-4395539	0.041	0.424
hsa-miR-145#-002149	0.036	0.426

TABLE 26

CSF miRNAs differentially expressed in PDDnoAD compared to ILBD (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold Change (PDDnoAD/ILBD)
hsa-miR-886-5p-4395304	0.024	4.734
hsa-miR-886-3p-4395305	0.022	4.189
hsa-miR-125a-3p-4395310	0.011	2.761
hsa-miR-222#-002097	0.040	2.635
hsa-miR-362-5p-4378092	0.006	2.392
hsa-miR-105-4395278	0.048	2.358
hsa-miR-363-4378090	0.036	2.203
hsa-let-7d-4395394	0.032	2.128
hsa-miR-143-4395360	0.011	0.329
hsa-miR-543-002376	0.034	0.430
hsa-miR-628-3p-002434	0.029	0.441
hsa-miR-26b#-002444	0.011	0.460
hsa-miR-146b-5p-4373178	0.035	0.494
hsa-miR-376c-4395233	0.035	0.497

TABLE 27

CSF miRNAs differentially expressed in PDDnoAD compared to PD (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold Change (PDDnoAD/PD)
hsa-miR-148b-4373129	0.005	4.709
hsa-miR-886-5p-4395304	0.013	3.754
hsa-miR-500-4395539	0.006	3.002
hsa-miR-886-3p-4395305	0.032	2.889
hsa-miR-519a-4395526	0.045	2.654
hsa-miR-511-4373236	0.035	2.279
hsa-miR-363-4378090	0.037	2.114
hsa-miR-99b-4373007	0.010	2.038
dme-miR-7-000268	0.015	0.118
hsa-miR-1233-002768	0.027	0.229
hsa-miR-409-3p-002332	0.034	0.248
hsa-miR-206-000510	0.027	0.263
hsa-miR-590-3P-002677	0.001	0.275
hsa-miR-213-000516	0.006	0.316
hsa-miR-629-001562	0.041	0.357
hsa-miR-539-4378103	0.037	0.385
hsa-miR-543-002376	0.004	0.407
hsa-miR-720-002895	0.014	0.438
hsa-miR-146b-5p-4373178	0.022	0.453
hsa-miR-136#-002100	0.013	0.465

TABLE 28

miRNAs Differentially Expressed in CSF Among Different Stages by the Unified Staging System for LBD (p < 0.05; at least 2 fold change) (87 in total).

Stages	0	2	3	4
0		22 (18, 4)	70 (46, 24)	9 (5, 4)
2	22 (18, 4)		20 (15, 5)	2 (0, 2)
3	70 (46, 24)	20 (15, 5)		29 (7, 22)
4	9 (5, 4)	2 (0, 2)	29 (7, 22)	

*Numbers in parentheses: numbers of (upregulated, downregulated) miRNAs.

TABLE 29

CSF miRNAs differentially expressed in Stage II compared to controls (corrected p values < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (Stage 2/0)
hsa-miR-664-002897	0.035	7.145
hsa-miR-126#-000451	0.041	6.557
hsa-miR-374b-4381045	0.023	5.102
hsa-miR-31-4395390	0.007	4.549
hsa-miR-1300-002902	0.032	3.927
hsa-miR-577-002675	0.032	3.690
hsa-miR-9#-002231	0.006	3.655
hsa-miR-497-001043	0.047	3.493
hsa-miR-660-4380925	0.025	3.394
hsa-miR-652-4395463	0.018	3.212
hsa-miR-31#-002113	0.032	2.830
hsa-miR-340-4395369	0.037	2.768
hsa-miR-200b-4395362	0.034	2.719
hsa-miR-26b#-002444	0.034	2.437
hsa-miR-135b-4395372	0.049	2.391
hsa-miR-195-4373105	0.003	2.243
hsa-miR-628-3p-002434	0.027	2.081
hsa-miR-29a#-002447	0.048	2.002
hsa-miR-671-3p-4395433	0.023	0.282
hsa-miR-142-3p-4373136	0.038	0.348
hsa-miR-145-4395389	0.043	0.407
hsa-miR-597-4380960	0.047	0.408

TABLE 30

CSF miRNAs differentiallly expressed in Stage III compared to controls (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (Stage 3/0)
hsa-miR-661-001606	0.008	35.493
hsa-miR-1300-002902	0.002	14.271
hsa-miR-497-001043	0.000	10.198
hsa-miR-664-002897	0.023	7.823
hsa-miR-577-002675	0.013	7.754
hsa-miR-9#-002231	0.003	7.611
hsa-miR-769-5p-001998	0.020	6.804
hsa-miR-374b-4381045	0.014	5.960
hsa-miR-31#-002113	0.004	5.909
hsa-miR-99a#-002141	0.002	5.850
hsa-miR-638-001582	0.014	5.810
hsa-miR-660-4380925	0.005	5.749
hsa-miR-1298-002861	0.037	5.389
hsa-miR-592-001546	0.018	4.821
rno-miR-29c#-001818	0.011	4.648
hsa-miR-324-5p-4373052	0.001	4.592
hsa-miR-590-3P-002677	0.001	4.436
hsa-miR-213-000516	0.004	4.032
hsa-miR-1271-002779	0.005	3.965
hsa-miR-9-4373285	0.034	3.796
hsa-miR-622-001553	0.017	3.549
hsa-miR-340#-002259	0.037	3.533
hsa-miR-151-5P-002642	0.035	3.373
hsa-miR-628-3p-002434	0.006	3.265
hsa-miR-29a-4395223	0.001	3.218
hsa-miR-143-4395360	0.046	3.190
hsa-miR-135b-4395372	0.013	3.045
hsa-miR-652-4395463	0.031	2.942
hsa-miR-129-3p-4373297	0.045	2.926
hsa-miR-218-4373081	0.004	2.880
hsa-miR-454-4395434	0.034	2.870
hsa-miR-340-4395369	0.028	2.834
hsa-miR-29c-4395171	0.001	2.802
hsa-miR-1226#-002758	0.030	2.670
hsa-miR-30a-3p-000416	0.012	2.617
hsa-miR-639-001583	0.042	2.574
hsa-miR-195-4373105	0.000	2.533
hsa-miR-191#-002678	0.007	2.389
hsa-miR-29a#-002447	0.030	2.254
hsa-miR-148b#-002160	0.020	2.173
hsa-miR-192-4373108	0.028	2.137
hsa-miR-148a-4373130	0.003	2.135

TABLE 30-continued

CSF miRNAs differentiallly expressed in Stage III compared to controls (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (Stage 3/0)
hsa-miR-548l-002909	0.036	2.055
hsa-miR-1264-002799	0.004	2.052
hsa-miR-19b-4373098	0.014	2.013
hsa-miR-27a#-002445	0.021	2.007
hsa-miR-483-3p-002339	0.005	0.081
hsa-miR-1260-002896	0.026	0.122
hsa-miR-296-5p-4373066	0.019	0.140
hsa-miR-145-4395389	0.001	0.161
hsa-miR-671-3p-4395433	0.009	0.166
hsa-miR-125a-5p-4395309	0.011	0.243
hsa-miR-197-4373102	0.005	0.257
hsa-miR-92a-4395169	0.002	0.284
hsa-miR-597-4380960	0.022	0.292
hsa-miR-328-4373049	0.001	0.305
hsa-miR-484-4381032	0.002	0.319
hsa-miR-125b-4373148	0.009	0.363
hsa-miR-345-4395297	0.019	0.413
hsa-miR-10b-4395329	0.008	0.461
hsa-miR-365-4373194	0.039	0.463
hsa-miR-98-4373009	0.008	0.464
hsa-miR-545-4395378	0.020	0.468
hsa-miR-28-3p-4395557	0.000	0.469
hsa-miR-25-4373071	0.006	0.472
hsa-miR-654-3p-4395350	0.009	0.474
hsa-miR-486-5p-4378096	0.033	0.475
hsa-miR-196b-4395326	0.014	0.482
hsa-miR-193a-5p-4395392	0.050	0.486
hsa-miR-199a-5p-4373272	0.040	0.497

TABLE 31

CSF miRNAs differentially expressed in Stage IV compared to controls (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (Stage 4/0)
hsa-miR-664-002897	0.0267	6.6111
hsa-miR-374b-4381045	0.0298	4.2124
hsa-miR-1300-002902	0.0443	3.9213
hsa-miR-9#-002231	0.0246	2.8799
hsa-miR-191#-002678	0.0377	2.2135
hsa-miR-142-3p-4373136	0.0103	0.2291
hsa-miR-197-4373102	0.0326	0.4014
hsa-miR-518a-3p-4395508	0.0247	0.4188
hsa-miR-320B-002844	0.0210	0.4882

TABLE 32

CSF miRNAs differentially expressed in Stage III compared to Stage II (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (Stage 3/2)
hsa-miR-661-001606	0.014	10.926
hsa-miR-638-001582	0.018	4.388
hsa-miR-144#-002148	0.002	4.147
hsa-miR-566-001533	0.010	3.230
hsa-miR-622-001553	0.022	3.205
hsa-miR-497-001043	0.031	2.919
hsa-miR-663B-002857	0.024	2.748
hsa-miR-1226#-002758	0.023	2.555
hsa-miR-30a-3p-000416	0.002	2.417
hsa-miR-324-5p-4373052	0.040	2.290
hsa-miR-590-3P-002677	0.042	2.244
rno-miR-29c#-001818	0.044	2.193
hsa-miR-148a-4373130	0.015	2.140
hsa-miR-31#-002113	0.023	2.088

TABLE 32-continued

CSF miRNAs differentially expressed in Stage III compared to Stage II (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (Stage 3/2)
hsa-miR-218-4373081	0.029	2.077
hsa-miR-483-3p-002339	0.011	0.142
hsa-miR-125b-4373148	0.001	0.251
hsa-miR-125a-5p-4395309	0.013	0.272
hsa-miR-145-4395389	0.015	0.395
hsa-miR-130b-4373144	0.047	0.448

TABLE 33

CSF miRNAs differentially expressed in Stage IV compared to Stage II (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (Stage 4/2)
hsa-miR-181a-4373117	0.022	0.436
hsa-miR-338-3p-4395363	0.049	0.459

TABLE 34

CSF miRNAs differentially expressed in Stage IV compared to Stage III (corrected p value < 0.05, fold change > 2 folds)

miRNAs	p-value	Fold change (Stage 4/3)
hsa-miR-483-3p-002339	0.041	5.103
hsa-miR-145-4395389	0.001	4.830
hsa-miR-296-5p-4373066	0.033	4.172
hsa-miR-125a-5p-4395309	0.010	3.893
hsa-miR-671-3p-4395433	0.022	3.134
hsa-miR-125b-4373148	0.001	2.949
hsa-miR-484-4381032	0.014	2.231
hsa-miR-661-001606	0.010	0.142
hsa-miR-497-001043	0.007	0.216
hsa-miR-1291-002838	0.004	0.240
hsa-miR-638-001582	0.013	0.244
hsa-miR-31#-002113	0.004	0.245
hsa-miR-378-002243	0.013	0.267
hsa-miR-1271-002779	0.002	0.267
hsa-miR-219-2-3p-4395501	0.033	0.272
hsa-miR-622-001553	0.010	0.289
hsa-miR-99a#-002141	0.007	0.294
hsa-miR-144#-002148	0.024	0.324
hsa-miR-769-5p-001998	0.037	0.325
hsa-miR-6638-002857	0.025	0.361
hsa-miR-1226#-002758	0.011	0.363
hsa-miR-142-3p-4373136	0.033	0.379
hsa-miR-151-5P-002642	0.001	0.382
hsa-miR-3208-002844	0.000	0.413
hsa-miR-12558-002801	0.044	0.417
hsa-miR-660-4380925	0.006	0.439
hsa-miR-192-4373108	0.045	0.479
hsa-miR-218-4373081	0.026	0.485
hsa-miR-30a-3p-000416	0.026	0.493

We also identified expressions of 26 miRNAs are correlated with the global Lewy-type asynucleinopathy (LTS) scores; 36 miRNAs are correlated with the degree of depigmentation of the neurons in Substantia Nigra; 40 miRNAs are correlated with the worsening of the motor functions, Unified PD Rating System (UPDRS) (Tables 35-38).

TABLE 35

Disease-correlated miRNAs in CSF (p < 0.05)

	By LTS Score*	By SN depigmentation score	By UPDRS**
Positively correlated	23	19	9
Negatively correlated	3	17	31

*LTS score: global Lewy-type α-synucleinopathy (LTS) scores.
**UPDRS: Unified PD Rating Scale.

TABLE 36

CSF miRNAs whose expression levels are correlated with Lewy-type a-synucleinopathy (LTS) scores (p < 0.05)

miRNAs	r
hsa-miR-664-002897	0.519
hsa-miR-148b#-002160	0.496
hsa-miR-29a#-002447	0.453
hsa-miR-592-001546	0.403
hsa-miR-363-4378090	0.400
hsa-miR-135b-4395372	0.397
hsa-miR-135a-4373140	0.390
hsa-miR-1298-002861	0.389
hsa-miR-34a#-002316	0.389
hsa-miR-374b-4381045	0.384
rno-miR-7#-001338	0.381
hsa-miR-590-3P-002677	0.379
rno-miR-29c#-001818	0.371
hsa-miR-1264-002799	0.371
hsa-miR-22#-002301	0.358
hsa-miR-30a-3p-000416	0.353
hsa-miR-650-001603	0.346
hsa-miR-340-4395369	0.338
hsa-miR-454-4395434	0.336
hsa-miR-767-3p-001995	0.333
hsa-miR-101#-002143	0.329
hsa-miR-190-4373110	0.328
hsa-miR-213-000516	0.320
hsa-miR-486-5p-4378096	−0.373
hsa-miR-196b-4395326	−0.435
hsa-miR-518a-3p-4395508	−0.439

TABLE 37

CSF miRNAs whose expression levels are correlated with SN depigmentation scores (p < 0.05)

miRNAs	r
hsa-miR-363-4378090	0.443
hsa-miR-374b-4381045	0.395
hsa-miR-184-4373113	0.339
hsa-miR-135b-4395372	0.325
hsa-miR-628-5p-4395544	0.323
hsa-miR-374a-4373028	0.309
hsa-miR-331-3p-4373046	0.294
hsa-miR-217-4395448	0.289
hsa-miR-590-5p-4395176	0.286
hsa-miR-664-002897	0.285
hsa-let-7a-4373169	0.279
hsa-miR-26b-4395167	0.272
hsa-let-7f-4373164	0.263
hsa-miR-362-5p-4378092	0.263
hsa-miR-455-3p-4395355	0.262
hsa-miR-449b-4381011	0.262
hsa-miR-99a-4373008	0.255
hsa-miR-135a-4373140	0.254
hsa-miR-26a-4395166	0.253
hsa-miR-218-2#-002294	−0.227
hsa-miR-139-3p-4395424	−0.232
hsa-miR-143#-002146	−0.246
hsa-miR-185-4395382	−0.249
hsa-miR-630-001563	−0.255

TABLE 37-continued

CSF miRNAs whose expression levels are correlated with SN depigmentation scores ($p < 0.05$)

miRNAs	r
hsa-miR-519a-4395526	−0.255
hsa-miR-376a#-002127	−0.260
hsa-let-7c-4373167	−0.263
hsa-miR-133b-4395358	−0.271
hsa-miR-145#-002149	−0.282
hsa-miR-181a-4373117	−0.299
hsa-miR-182#-000483	−0.308
hsa-miR-200a#-001011	−0.313
hsa-miR-197-4373102	−0.315
hsa-miR-146a#-002163	−0.318
hsa-miR-142-3p-4373136	−0.354
hsa-miR-518a-3p-4395508	−0.363

TABLE 38

CSF miRNAs whose expression levels are correlated with UPDRS ($p < 0.05$)

miRNAs	r
hsa-miR-101#-002143	0.572
hsa-miR-222#-002097	0.565
hsa-miR-626-001559	0.555
hsa-miR-29a#-002447	0.503
hsa-miR-1238-002927	0.469
hsa-miR-1260-002896	0.453
hsa-miR-363#-001283	0.393
hsa-miR-1244-002791	0.388
hsa-miR-567-001534	0.385
hsa-miR-101-4395364	−0.230
hsa-miR-218-4373081	−0.233
hsa-miR-27a#-002445	−0.234
hsa-miR-330-3p-4373047	−0.236
hsa-miR-30e-3p-000422	−0.237
hsa-miR-29b-2#-002166	−0.239
hsa-miR-411-4381013	−0.241
hsa-miR-875-5p-002203	−0.242
hsa-miR-337-5p-4395267	−0.244
hsa-miR-130a-4373145	−0.245
hsa-miR-454#-001996	−0.257
dme-miR-7-000268	−0.261
hsa-miR-19b-1#-002425	−0.263
hsa-miR-32-4395220	−0.263
hsa-miR-137-4373301	−0.265
hsa-miR-122-4395356	−0.268
hsa-miR-518a-3p-4395508	−0.269
hsa-miR-219-5p-4373080	−0.274
hsa-let-7b-4395446	−0.278
hsa-miR-655-4381015	−0.279
hsa-miR-1264-002799	−0.282
hsa-miR-1262-002852	−0.289
hsa-miR-518b-4373246	−0.290
hsa-miR-152-4395170	−0.292
hsa-miR-338-3p-4395363	−0.294
hsa-miR-520D-3P-002743	−0.316
hsa-miR-488-4395468	−0.354
hsa-miR-551b-4380945	−0.375
hsa-miR-625-4395542	−0.382
hsa-miR-519a-4395526	−0.419
hsa-miR-21-4373090	−0.429

More importantly, we identified a series of miRNA signatures as first generation of diagnostic biomarkers for PD and the progression of PD:

1) miRNA signature composed by 14 miRNAs that distinguishes ILBD to normal controls, which may be used as a diagnostic biomarker for pre-symptomatic PD (FIG. **5**): miR-516, miR-191#, miR-449b, miR-497, miR-628, miR-213, miR-23a, miR-29#, miR-488, miR-597, miR-296-5p, miR-671-3p, miR-654-3p, miR-99#;

2) miRNA signature composed of 13 miRNAs that distinguishes normal control subjects from PD, which may be used as a diagnostic biomarker for diagnosis of early PD (FIG. **6**): miR-590-3p, miR-213, miR-9#, miR-191#, miR-497, miR-664, miR-99a#, miR-1183, miR-340#, miR-628-3p, miR-7#, miR-29a#, miR-142-3p;

3) miRNA signature composed by 6 miRNAs that distinguishes ILBD from PD, which may change from asymptomatic Lewis Body disease to symptomatic PD, and may be used as a diagnostic biomarker for diagnosis of early PD (FIG. **7**): miR-664, miR-1285, miR-1183, miR-143, miR-519a, miR-603;

4) miRNA signature composed by 8 miRNAs that distinguish clinically normal subjects (including normal control and ILBD subjects), which may also be used early diagnostic biomarkers for PD (FIG. **8**): miR-590-3p, miR-664, miR-519a, miR-340*, miR-720, miR-142-3p, miR-185, and miR-213; and

5) miRNA signature composed by 7 miRNAs which distinguish PD from PD with dementia, and may be used as a diagnostic biomarker for cognitive impairment in PD patients (FIG. **9**): miR-590-3p, miR-213, miR-409-3p, miR-500, miR-7, miR-206 and miR-629.

Example 3

miR-212 and miR-132 Play Important Roles in Pathogenesis of PD and are Novel Therapeutic Targets for Treatment of PD and L-Dopa-Induced Dyskinesia

Among the miRNAs in the putamen, which are correlated with the progression of disease, miR-212 and miR-132 are highly expressed the putamen, and are significantly increased (~1.6 fold) in the putamen of PD cases, compared to controls (FIG. **8**). miR-212 and miR-132 are clustered in intron 1 of a highly-conserved, non-coding RNA gene on human chromosome 1p13.3, and have high sequence homology with the same seed sequences, therefore, share most of their downstream targets and functions (FIG. **10**). Interestingly, mature miR-132 is expressed at a much higher level than miR-212 in the putamen (>60 fold), suggesting that miR-132 plays a major role in the putamen.

Correlation study with all cases regardless of their clinical diagnosis showed that levels of miR-212 and miR-132 expression in the putamen are significantly correlated to the global Lewy-type α-synucleinopathy (LTS) scores and the degree of substantia nigra (SN) pigmented neuron loss score (FIG. **11**), with the highest correlation scores among all differentially expressed miRNAs, strongly suggesting that expression of miR-212 and/or miR-132 correlates with SN neurodegeneration and PD pathology, and that misregulation of miR-212 and/or miR-132 are involved in PD. Multiple lines of evidence support that miR-212 and/or miR-132 play important roles in pathogenesis of PD and are novel therapeutic targets for treatment of PD and L-Dopa-induced dyskinesia:

1) Our target prediction analysis showed that Nurr1, a member of nuclear receptor superfamily, is a predicted target of miR-212 and/or miR-132. Nurr1 is essential for the differentiation and survival of nigral dopaminergic neurons5-7. Mutations are associated with PD. Therefore, miR-212 and/or miR-132 may regulate the function and survival of dopaminergic (DA) neurons by modulating Nurr1.

2) Our functional annotation analysis of predicted target genes of miR-212 and miR-132 revealed significant enrichment of genes involved in neurotrophin signaling ($p=0.01$),

MAPK signaling (p=0.008) and longterm potentiation (p=0.02), consistent with reports that miR-212 and miR-132 are neurotrophin- and activity-regulated miRNAs and are important for neural plasticity.

3) NMDA receptors (NMDA-Rs) are shown to mediate neurotrophin- and activity-induced induction of miR-212 and miR-132. In PD, depletion of nigrostriatal DA results in relative glutamatergic overactivity in the striatum, which plays central roles in PD as well as L-dopa induced dyskinesia. Therefore, upregulation of miR-212 and/or miR-132 in PD putamen may be a result of loss of dopamine input and relative overactivity through NMDA-R;

4) miR-212 and miR-132 are shown to target Methyl CpG-binding protein-2 (MeCP2), which promote the expression of brain-derived neurotrophic factor (BDNF), a potent trophic factor for DA neurons, which has been shown to be decreased in substantia nigra (SN) and striatum PD patients and animal models. Therefore, increased of expression of miR-212 and/or miR-132 may inhibit the expression of MeCP2 and BDNF, and contribute to the pathogenesis of PD;

5) miR-212 and miR-132 are shown to promote NF-κB- and p53-activation through repression of silent information regulator 1 (SIRT1), a NAD+-dependent deacetylase, which deacetylates and inactivates p53 and the p65 subunit of NF-κB29-32. Increased p53 and NF-κB activation in SN and striatum promote cellular senescence and apoptosis. Therefore, miR-212 and/or miR-132 may contribute to nigrostriatal neurodegeneration through modulating NF-κB and p53 activation.

Collectively, these data suggest that upregulation of miR-212 and/or miR-132 in the putamen may be a result of loss of nigrostriatal DA and overactivation of NMDA-Rs; miR-212 and/or miR-132 may mediate NMDAR overactivation-induced excitotoxicity and play important roles in the pathogenesis of PD through argeting MeCP2, SIRT1 and Nurr1, modulating Nurr1-, BDNF-, NF-κB- and p53-involved pathogenetic pathways. Therefore, prevention of loss of DA innervation-resulted upregulation of miR-212 and/or miR-132 may be neuroprotective for the nigrostriatal system and prevent the development of PD. miR-212 and/or miR-132 may be novel therapeutic targets for the treatment of PD.

The above Figures and disclosure are intended to be illustrative and not exhaustive. This description will suggest many variations and alternatives to one of ordinary skill in the art. All such variations and alternatives are intended to be encompassed within the scope of the attached claims. Those familiar with the art may recognize other equivalents to the specific embodiments described herein which equivalents are also intended to be encompassed by the attached claims.

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<400> SEQUENCE: 51

cgugccaccc uuuuccccag 20

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<400> SEQUENCE: 52

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<400> SEQUENCE: 53

cuuccucguc ugucugcccc 20

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<400> SEQUENCE: 54

aaguaguugg uuuguaugag augguu 26

<210> SEQ ID NO 55
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<400> SEQUENCE: 56

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<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 58

aggcauugac uucucacuag cu 22

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<400> SEQUENCE: 59

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<400> SEQUENCE: 62

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<400> SEQUENCE: 66

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<400> SEQUENCE: 67

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<400> SEQUENCE: 68

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<400> SEQUENCE: 69

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<223> OTHER INFORMATION: Synthetic hsa-miR-1290-002863

<400> SEQUENCE: 70

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<400> SEQUENCE: 71

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<210> SEQ ID NO 72
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<400> SEQUENCE: 72

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<400> SEQUENCE: 73

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<400> SEQUENCE: 74

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<210> SEQ ID NO 75
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<400> SEQUENCE: 76

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<400> SEQUENCE: 77

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<400> SEQUENCE: 78

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<210> SEQ ID NO 80
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<400> SEQUENCE: 81

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<210> SEQ ID NO 82
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<400> SEQUENCE: 82

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<210> SEQ ID NO 83
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<400> SEQUENCE: 83

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<210> SEQ ID NO 84
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<400> SEQUENCE: 84

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<210> SEQ ID NO 85
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<400> SEQUENCE: 85

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<400> SEQUENCE: 86

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<210> SEQ ID NO 87
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<400> SEQUENCE: 87

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<210> SEQ ID NO 88
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<400> SEQUENCE: 88

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<400> SEQUENCE: 89

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<210> SEQ ID NO 90
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<400> SEQUENCE: 90

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<210> SEQ ID NO 91
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic hsa-miR-144#-002148

<400> SEQUENCE: 91

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<400> SEQUENCE: 93

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<400> SEQUENCE: 94

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<210> SEQ ID NO 95
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<400> SEQUENCE: 95

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<400> SEQUENCE: 99

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<400> SEQUENCE: 101

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<210> SEQ ID NO 103
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<220> FEATURE:
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<400> SEQUENCE: 106

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<212> TYPE: RNA
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<400> SEQUENCE: 107

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<400> SEQUENCE: 110

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<210> SEQ ID NO 111
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<400> SEQUENCE: 111

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<210> SEQ ID NO 113
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<400> SEQUENCE: 113

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<210> SEQ ID NO 115
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<400> SEQUENCE: 115

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<210> SEQ ID NO 116
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<400> SEQUENCE: 116

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<400> SEQUENCE: 117

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<210> SEQ ID NO 119
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<400> SEQUENCE: 119

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<210> SEQ ID NO 120
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<400> SEQUENCE: 120

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<400> SEQUENCE: 121

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<210> SEQ ID NO 122
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<210> SEQ ID NO 123

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<211> LENGTH: 22
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<400> SEQUENCE: 123

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<210> SEQ ID NO 124
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<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 124

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<210> SEQ ID NO 125
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<400> SEQUENCE: 125

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<400> SEQUENCE: 126

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<210> SEQ ID NO 127
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<400> SEQUENCE: 127

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<400> SEQUENCE: 128

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<210> SEQ ID NO 129
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<210> SEQ ID NO 131
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<400> SEQUENCE: 133

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<210> SEQ ID NO 134
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<210> SEQ ID NO 135
<211> LENGTH: 22
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<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 136

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<210> SEQ ID NO 137
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<210> SEQ ID NO 210
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<210> SEQ ID NO 211
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<400> SEQUENCE: 213

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<210> SEQ ID NO 214
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<400> SEQUENCE: 217

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<400> SEQUENCE: 222

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<210> SEQ ID NO 224
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<223> OTHER INFORMATION: Synthetic hsa-miR-566-001533

<400> SEQUENCE: 224

gggcgccugu gaucccaac 19

<210> SEQ ID NO 225
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<400> SEQUENCE: 225

ugaguuggcc aucugaguga g 21

<210> SEQ ID NO 226
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<212> TYPE: RNA
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<400> SEQUENCE: 226

cacgcucaug cacacaccca ca 22

<210> SEQ ID NO 227
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<400> SEQUENCE: 227

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<210> SEQ ID NO 228
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<223> OTHER INFORMATION: Synthetic hsa-miR-582-3p-4395510

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<210> SEQ ID NO 229
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<400> SEQUENCE: 229

ucagaacaaa ugccgguucc caga 24

<210> SEQ ID NO 230
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uaauuuuaug uauaagcuag u 21

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<400> SEQUENCE: 231

gagcuuauuc auaaaagugc ag 22

<210> SEQ ID NO 232
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 232

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<210> SEQ ID NO 233
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<400> SEQUENCE: 233

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<210> SEQ ID NO 234
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<400> SEQUENCE: 234

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<210> SEQ ID NO 235
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<400> SEQUENCE: 235

uggucuagga uuguuggagg ag 22

<210> SEQ ID NO 236
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<400> SEQUENCE: 236

aggcugcgga auucaggac 19

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<400> SEQUENCE: 238

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<400> SEQUENCE: 239

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<400> SEQUENCE: 240

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<223> OTHER INFORMATION: Synthetic hsa-miR-622-001553

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<400> SEQUENCE: 241

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<400> SEQUENCE: 242

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<400> SEQUENCE: 246

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<210> SEQ ID NO 247
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<400> SEQUENCE: 247

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<210> SEQ ID NO 248
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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic hsa-miR-635-001578

<400> SEQUENCE: 248

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<210> SEQ ID NO 249
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic hsa-miR-638-001582

<400> SEQUENCE: 249

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<400> SEQUENCE: 250

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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic hsa-miR-641-001585

<400> SEQUENCE: 251

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<210> SEQ ID NO 252
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic hsa-miR-644-001596

<400> SEQUENCE: 252

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<210> SEQ ID NO 253
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<400> SEQUENCE: 253

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<212> TYPE: RNA
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<400> SEQUENCE: 254

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<400> SEQUENCE: 255

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<223> OTHER INFORMATION: Synthetic hsa-miR-659-001514

<400> SEQUENCE: 256

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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic hsa-miR-660-4380925

<400> SEQUENCE: 257

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<210> SEQ ID NO 258
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic hsa-miR-661-001606

<400> SEQUENCE: 258

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<400> SEQUENCE: 259

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<210> SEQ ID NO 260
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<400> SEQUENCE: 260

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<210> SEQ ID NO 261
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic hsa-miR-671-3p-4395433

<400> SEQUENCE: 261

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<212> TYPE: RNA
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<400> SEQUENCE: 263

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<212> TYPE: RNA
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<400> SEQUENCE: 264

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<400> SEQUENCE: 267

gcaggaacuu gugagucucc u 21

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<400> SEQUENCE: 268

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<223> OTHER INFORMATION: Synthetic hsa-miR-885-5p-4395407

<400> SEQUENCE: 269

uccauuacac uacccugccu cu 22

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<212> TYPE: RNA
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<223> OTHER INFORMATION: Synthetic hsa-miR-886-3p-4395305

<400> SEQUENCE: 270

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<400> SEQUENCE: 271

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<400> SEQUENCE: 272

auaaagcuag auaaccgaaa gu 22

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<400> SEQUENCE: 274

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<220> FEATURE:
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<400> SEQUENCE: 276

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic hsa-miR-9-4373285

<400> SEQUENCE: 277

ucuuugguua ucuagcugua uga 23

<210> SEQ ID NO 278
<211> LENGTH: 22
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<220> FEATURE:
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<400> SEQUENCE: 278

ugagguagua aguuguauug uu 22

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caagcucgcu ucuaugggguc ug 22

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cacccguaga accgaccuug cg 22

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<400> SEQUENCE: 281

cuauacgacc ugcugccuuu cu 22

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<400> SEQUENCE: 282

ugaccgauuu cuccuggugu uc 22

<210> SEQ ID NO 283
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic rno-miR-7#-001338

<400> SEQUENCE: 283

caacaaauca cagucugcca ua 22

I claim:

1. A method of identifying a subject at risk of developing or having Parkinson's Disease (PD), the method comprising:

a) isolating a biological sample from the subject;

b) detecting a level of expression in a miRNA signature in the biological sample from the subject, the miRNA signature comprising a plurality of miRNAs;

the plurality of miRNAs comprising:

i) SEQ ID NOs: 204, 110, 192, 200, 244, 2, 134, 144, 198, 234, 143, 261, 255, and 179 (miR-516-3p, miR-191#, miR-449b, miR-497, miR-628-3p, miR-213, miR-23a, miR-29a#, miR-488, miR-597, miR-296-5p, miR-671-3p, miR-654-3p, and miR-99a#);

ii) SEQ ID NOs: 1-13, (miR-590-3p, miR-213, miR-9#, miR-191#, miR-497, miR-664, miR-99a#, miR-1183, miR-340#, miR-628-3p, miR-7#, miR-29a#, miR-142-3p);

iii) SEQ ID NOs: 14-20 and 2 (miR-590-3p, miR-664, miR-519a, miR-340#, miR-720, miR-142-3p, miR-185, and miR-213); or

iv) SEQ ID NOs: 28, 2 and 30-34 (miR-590-3p, miR-213, miR-409-3p, miR-500, miR-7, miR-206, and miR-629);

c) comparing the level of expression of the plurality of miRNAs in the sample to a level of expression of the plurality of miRNAs in a reference,

wherein an increased or decreased level of expression in the sample compared to the level of expression in the reference for each of the plurality of miRNAs identifies the subject as having PD or who is at risk of developing PD.

2. The method of claim **1**, wherein the reference is a sample from a normal, healthy subject.

3. The method of claim **1**, wherein the plurality of miRNAs comprise SEQ ID NOs: 204, 110, 192, 200, 244, 2, 134, 144, 198, 234, 143, 261, 255, and 179 (miR-516-3p, miR-191#, miR-449b, miR-497, miR-628-3p, miR-213, miR-23a, miR-29a#, miR-488, miR-597, miR-296-5p, miR-671-3p, miR-654-3p, and miR-99a#) and the miRNA signature is indicative of pre-symptomatic PD.

4. The method of claim **1**, wherein the plurality of miRNAs comprise SEQ ID NOs: 1-13, (miR-590-3p, miR-213, miR-9#, miR-191#, miR-497, miR-664, miR-99a#, miR-1183, miR-340#, miR-628-3p, miR-7#, miR-29a#, miR-142-3p) and the miRNA signature is indicative of early PD.

5. The method of claim **1**, wherein the plurality of miRNAs comprise SEQ ID NOs: 14-20 and 2 (miR-590-3p, miR-664, miR-519a, miR-340#, miR-720, miR-142-3p, miR-185, and miR-213) and the miRNA signature is indicative of early PD.

6. The method of claim **1**, wherein the plurality of miRNAs comprise SEQ ID NOs: 28, 2 and 30-34 (miR-590-3p, miR-213, miR-409-3p, miR-500, miR-7, miR-206, and miR-629) and the miRNA signature is indicative of cognitive impairment of PD.

* * * * *